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(71) Applicant: **DUPONT PHARMACEUTICALS COMPANY** [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilmington, DE 19805 (US).

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(72) Inventor: **LIU, Shuang**; 17 Judith Road, Chelmsford, MA 01824 (US).

(74) Agent: **DOLAN, Peter, L.**; Dupont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).



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(54) Title: **MACROCYCLIC CHELANTS FOR METALLOPHARMACEUTICALS**

(57) Abstract: This invention relates to new macrocyclic chelants and metal chelates thereof, methods of preparing the chelants and metal chelates, and pharmaceutical compositions comprising the macrocyclic chelants and metal chelates. This invention relates particularly to the use of the new metal chelates as contrast agents in X-ray or CT, MRI imaging, and radiopharmaceuticals for the diagnosis of cardiovascular disorders, infectious disease and cancer. This invention also relates to new bifunctional chelants (BFCs) for attaching diagnostic metals and therapeutic isotopes to target-specific biomolecules such as proteins, peptides, peptidomimetics, and non-peptide receptor ligands. In addition, the macrocyclic chelants are useful for heavy metal detoxification.

MACROCYCLIC CHELANTS FOR METALLOPHARMACEUTICALS

FIELD OF THE INVENTION

5 This invention relates to new macrocyclic chelants and metal chelates thereof, methods of preparing the chelants and metal chelates, and pharmaceutical compositions comprising the macrocyclic chelants and metal chelates. This invention relates particularly to
10 the use of the new metal chelates as contrast agents in X-ray or CT, MRI imaging, and radiopharmaceuticals for the diagnosis of cardiovascular disorders, infectious disease and cancer. This invention also relates to new bifunctional chelants (BFCs) for attaching diagnostic
15 metals and therapeutic isotopes to target-specific biomolecules such as proteins, peptides, peptidomimetics, and non-peptide receptor ligands. In addition, the macrocyclic chelants are useful for heavy metal detoxification.

20

BACKGROUND OF THE INVENTION

Medical imaging modalities, such as MRI, X-ray, gamma scintigraphy, and CT scanning, have become extremely important tools in the diagnosis and treatment
25 of various diseases and illness. Imaging of internal body parts relies on the contrast between the targeted organ and the surrounding tissues. The targeted organs or tissues are visible by the use of a particular metallopharmaceutical contrast agent. In X-ray and CT
30 diagnostics, increased contrast of internal organs, such as kidney, the urinary tract, the digestive tract, cardiovascular system, tumors, and so forth is obtained

by administering a contrast agent which is substantially radiopaque. In conventional proton MRI diagnostics, increased contrast of internal organs and tissues may be obtained by administering compositions containing
5 paramagnetic metal species, which increase the relaxivity of surrounding water protons. In ultrasound diagnostics, improved contrast is obtained by administering compositions having acoustic impedances different from that of blood and other tissues. In
10 gamma scintigraphy, contrast of internal organ is obtained by the specific localization of a gamma ray emitting radiopharmaceutical.

Attachment of metal ions to biomolecules (BM) such as antibodies, antibody fragments, peptides,
15 peptidomimetics, and non-peptide receptor ligands leads to useful target-specific diagnostic and therapeutic metallopharmaceuticals. These include fluorescent, radioactive and paramagnetic metal ions attached to proteins that can be used as probes in vivo in
20 biological systems and in vitro in analytical systems as radioimmunoassays. For example, attachment of radionuclides to monoclonal antibodies that recognize tumor associated antigens provides radioimmunoconjugates useful for cancer diagnosis and therapy. The monoclonal
25 antibodies are used as carriers of desired radioisotope to the tumor in vivo.

Radiopharmaceuticals can be classified into two primary classes: those whose biodistribution is determined exclusively by their chemical and physical
30 properties; and those whose ultimate distribution is determined by receptor binding or other biological interactions. The latter class is often called target-

specific radiopharmaceuticals. In general, a target specific radiopharmaceutical can be divided into four parts: a targeting molecule, a linker, a BFC, and a radionuclide. The targeting molecule serves as a
5 vehicle, which carries the radionuclide to the receptor site at the diseased tissue or organ. The targeting molecules can be macromolecules such as antibodies; they can also be small biomolecules: peptides, peptidomimetics, and non-peptide receptor ligands. The
10 choice of biomolecule depends upon the targeted disease or disease state. The radionuclide is the radiation source. The selection of radionuclide depends on the intended medical use (diagnostic or therapeutic) of the radiopharmaceutical. Between the targeting molecule and
15 the radionuclide is the BFC, which binds strongly to the metal ion and is covalently attached to the targeting molecule either directly or through a linker. Selection of a BFC is largely determined by the nature and oxidation state of the metallic radionuclide. The
20 linker can be a simple hydrocarbon chain or a long poly(ethylene glycol) (PEG), which is often used for modification of pharmacokinetics. Sometimes, an anionic poly (amino acid) is used to increase the blood clearance and to reduce the background activity, thereby
25 improving the target-to-background ratio.

The use of metallic radionuclides offers many opportunities for designing new radiopharmaceuticals by modifying the coordination environment around the metal with a variety of chelants. The coordination chemistry
30 of the metallic radionuclide will determine the geometry and solution stability of the metal chelate. Different metallic radionuclides have different coordination chemistries, and require BFCs with different donor atoms

and ligand frameworks. For "metal essential" radiopharmaceuticals, the biodistribution is exclusively determined by the chemical and physical properties of the metal chelate. For target-specific
5 radiopharmaceuticals, however, the "metal label" is not totally innocent because the target uptake and biodistribution will be affected by not only the targeting biomolecule but also the metal chelate and the linker. This is especially true for
10 radiopharmaceuticals based on small molecules such as peptides due to the fact that in many cases the metal chelate contributes greatly to the overall size and molecular weight. Therefore, the design and selection of the BFC is very important for the development of a
15 new radiopharmaceutical.

The same principle used for target-specific metallo-radiopharmaceuticals also applies to target-specific MRI contrast and ultrasound agents. Unlike the target-specific metalloradiopharmaceutical, where the
20 excess unlabeled biomolecule can compete with the radiolabeled BFC-BM conjugate and block the docking of the radiolabeled receptor ligand, MRI and ultrasound contrast agents contain no excess unlabeled BFC-BM conjugate. Saturation of the receptor sites will
25 maximize the contrast between the diseased tissues and normal tissue provided that the use of a relatively large amount of metal-BFC-BM chelate does not cause unwanted side effects.

For a therapeutic radiopharmaceutical or an MRI
30 contrast agent, it is especially important to keep the metal chelate intact under physiological conditions, particularly in the presence of native chelators, such

as transferrin, which have very high affinity for trivalent lanthanide metal ions. This requires the chelant to form metal chelate with high thermodynamic stability and kinetic inertness.

5 Several BFC systems such as ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA), as well as their derivatives, have been reported to form thermodynamically stable metal chelates. EDTA-based
10 BFCs were first developed by Sunberg et al (*Nature* **1974**, 250, 587) in the 1970s. Krejcarek and Tucker (*Biochem. Biophys. Res. Commun.* **1976**, 77, 581) developed an activated DTPA analog via a mixed anhydride, which can be linked to proteins. Later, Hnatowich et al (*Science*
15 **1983**, 220, 613) used the cyclic anhydride of DTPA for the same purpose. These linear BFCs bond to a variety of metal ions like ^{111}In or ^{90}Y and form thermodynamically stable metal chelates. However, metal
20 chelates of linear BFCs are kinetically labile, which contributes to the loss of radionuclide from the metal chelate and often leads to severe bone marrow toxicity. Gansow et al (*Bioconjugate Chem.* **1991**, 2, 187; *Inorg. Chem.* **1986**, 25, 2772) prepared a series of substituted DTPA analogs, which form metal chelates with improved
25 solution stability.

Polyaza macrocycles have been widely used as chelants for a variety of transition metals. The macrocyclic polyaminocarboxylates such as 1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetracetic acid (DOTA)
30 and 1,4,8,11-tetraazacyclo-tetradecane-1,4,8,11-tetracetic acid (TETA) are known to form highly stable metal chelates due to their highly preorganized

macrocyclic ligand framework. Their Gd chelates have been widely studied as MRI contrast agents. Examples include gadolinium complexes Gd-DOTA (DotaremTM, Guerbet/France), Gd-HP-DO3A (ProHanceTM, Bracco/Italy),
5 and Gd-DO3A-butrol (GadovistTM, Schering/Germany).

Macrocyclic chelants such as DOTA have also been used as BFCs for the radiolabeling of proteins (antibodies or antibody fragments) and peptides with various diagnostic and therapeutic radionuclides (such
10 as ¹¹¹In and ⁹⁰Y). Meares and coworkers were the first to synthesize macrocyclic BFCs (*Anal. Biochem.* **1985**, 148, 249; *Nucl. Med. Biol.* **1986**, 13, 363; *Inorg. Chem.* **1987**, 26, 3458), which form ⁶⁷Cu and ⁹⁰Y chelates with high thermodynamic stability and kinetic inertness.
15 Macrocyclic chelants with three-dimensional cavities are of particular interest because of the high stability of the metal chelates, the substantial selectivity for certain metal ions, either by enforcing a specific spatial arrangement of donor atoms or by introducing
20 different donor atoms into the ligand backbone, and their capability to adopt a preorganized conformation in the unchelated form. The higher the degree of preorganization of an unchelated ligand, the more stable the complex is.

25 Preorganization of a polydentate chelant results in not only the high thermodynamic stability but also the increased kinetic inertness of its metal chelate. This has been exemplified by the fact that the half-life for [Gd(DOTA)]⁻ in 0.1 M HCl is 60.2 h and 2000 years at pH =
30 6.4 while the complex [Gd(DTPA)]²⁻ having comparable thermodynamic stability decomposes rapidly under acidic conditions with a half-life of ~1.0 min. The highly

preorganized macrocyclic framework of DOTA forces four acetate chelating arms to adopt such a conformation that the metal ion can be completely wrapped by an N_4O_4 donor set. At the same time, this also makes it more
5 difficult for the coordinated acetate to be dissociated from the metal center. Therefore, preorganization should be an important factor in the design of new BFCs for the radiolabeling of biomolecules.

Generally, there are three possible approaches to
10 attach a biomolecule to a DOTA-based chelant. In the first approach, the attachment is at one of the carbon atoms of the macrocyclic chelator backbone. In principle, this will result in formation of eight possible isomers when coordinated to the lanthanide
15 metal ion. In the second approach, the linker is attached to the methylene-carbon atom of one of four acetate chelating arms, which may also result in formation of eight possible isomeric forms. In both approaches, the conjugation of the biomolecule does not
20 lead to a significant change in the thermodynamic stability and kinetic inertness of the metal chelate as compared to those of the DOTA chelate. In the third approach, the biomolecule is conjugated to one of the four acetate groups via a CO-N amide bond. Compared to
25 the carboxylate-O, the carbonyl-O is a relatively weak donor for yttrium and lanthanide metal ions. This often leads to the lower thermodynamic stability of the corresponding metal chelate. However, the kinetic inertness of its metal complex remains relatively
30 unchanged.

In U.S. Patent No. 4,678,667, Meares et al disclosed a copper chelate conjugate for diagnostic or

therapeutic applications. The bifunctional macrocyclic chelants include substituted DOTA, TETA, TRITA, HETA. The linker is at least 8-atom in length and the attachment position of the linker is on the carbon atom of the polyamine macrocycle. In U.S. Patent No. 5,428,156 disclosed a method of producing DOTA, TETA, DOTA-NHS(NHS = N-hydroxysuccinimide) and TETA-NHS esters for conjugation of biomolecule. Meares et al (WO 95/26206 and U.S. Patent No. 5,958,374) also disclosed a method for preparing a radionuclide-labeled chelating agent complex. It specifically disclosed DOTA(Gly)₃-L-(p-isothiocyanato)-Phe-amide as the BFC. The pendant linkers also include -CH₂CO-(AA)_m-(AA-Phe-Gly), where AA represents an amino acid diradical, more preferably the glycine diradical -NHCH₂CO-. Gansow et al (WO 89/11475, WO 91/14458, U.S Patent Nos. 4,923,985 and 5,428,154) disclosed a process of making 4-aminophenyl-DOTA and its use a BFC for the radiolabeling of biomolecules such as antibody. Parker et al (WO 87/05030, WO89/01476, EP 0382583B1 and EP 0382583A1) disclosed a series of DOTA analogs as BFCs, which are coupled with biomolecules such as a protein, especially antibodies, peptides or carbohydrates to form conjugate compounds. The linker and conjugation group is attached to either one of the four acetate chelating arms or one of the carbon atom of the macrocyclic backbone. Watson, et al (WO 90/12050 and WO93/06868) disclosed polychelants and their metal chelates useful in diagnostic imaging and in radiotherapy. The macrocyclic chelant moieties are linked to the backbone moiety (dendrimer or polylysine) via an amide-bond. In U.S. Patent No. 5,053,053, Dean et al also disclosed a series of DOTA and DO3A analogs as BFCs. For DO3A-based BFCs, the conjugation group is

connected to a linker attached to one of the four amine-nitrogen atoms. For DOTA derivatives, the linker group is connected to either one of carbon-atoms on the macrocyclic backbone or the methylene-carbon atom of one of the four acetate chelating arms. Tweedle, et al (EP 0292689 A2/A3; U.S. Patent Nos. 4,885,363, 5,474,756, and 5,846,519) disclosed metal chelates, particularly those of neutral charge, for MRI contrast imaging. It also disclosed DO3A analogs as BFCs for the radiolabeling of biomolecules. Kruper et al (U.S. Patent Nos. 5,310,535 and 5,739,323) disclosed the DOTA analogs as BFCs for the radiolabeling of proteins. The linker is connected to the acetate chelating arm and the conjugation group is on a benzene ring. It was shown that the DOTA monoamide has better kinetic inertness because of less bone uptake. Kubomura et al (AU9335519 and EP 0565930A1) disclosed the use of DO3A-CH₂CONHCH₂CH₂NH₂ as the BFC, and the metal chelates of BFC-BM conjugates as diagnostic or therapeutic pharmaceuticals. Gozzini et al (WO 97/32862) disclosed a new class of polychelants, their chelates with metal ions and their physiologically acceptable salts, which can be used, either as they are or in association or formulation with other components, for diagnostic imaging in general or specific contrast agents for specific tissues, organs or body compartments. It specifically discloses DOTA as the BFC, and a process of making these macrocyclic chelants with DO3A-CH₂CONHCH₂CH₂CHO and poly(amino acids) as key intermediates. Wilson et al (U.S. Patent No. 5,756,065) also disclosed DOTA analogs as BFCs. The conjugation group is attached to a benzene ring and the linker group is connected to one of the four acetate chelating arms.

Almen et al. (U.S. Patent No. 5,348,954) discloses heterocyclic chelating agents for use in heavy metal detoxification. Watson (U.S. Patent No. 5,914,095) also discloses polychelants for use in metal detoxification.

5

SUMMARY OF THE INVENTION

The present invention provides macrocyclic chelants containing a substituted pyridinone moiety. These macrocyclic chelants are unique for several reasons.

10 The hydroxy group of the pyridinone heterocycle has a higher pKa value than the carboxylic group and the hydroxy-O is a better donor atom than the corresponding carbonyl-O atom in a DOTA-biomolecule conjugate when bonded to "hard" trivalent lanthanide metal ions. These

15 macrocyclic chelants will form anionic metal chelates with higher hydrophilicity, which is beneficial for improved pharmacokinetics. The pyridinone binding unit is bidentate, and is available to form a "pre-chelate" before the metal ion goes into the coordination cavity

20 of the macrocycle. This, in return, will result in improved radiolabeling kinetics. Like DOTA, the macrocyclic chelants are expected to form stable complexes with trivalent metal ions such as In^{3+} , Y^{3+} , Sm^{3+} , Gd^{3+} , Dy^{3+} , Ho^{3+} , Yb^{3+} , and Lu^{3+} . Unlike phenols,

25 the pyridinone ring is radiolytically stable, which is very important to maintain the solution stability of therapeutic radiopharmaceuticals.

The present invention also provides macrocyclic chelants containing a succinimide or phthalimide

30 functional group. The succinimide or phthalimide group is connected to one of the four amine-nitrogen atoms of the macrocycle via a $\text{C}_1\text{-C}_3$ alkylene linker in such a way

that the carbonyl-O atom of the succinamide or phthalimide group is available to coordinate the lanthanide metal ions to form 8- or 9-coordinated metal chelates. Unlike macrocyclic chelants with
5 substituent(s) on the acetate chelating arm or macrocyclic backbone, macrocyclic chelants containing a succinimide or phthalimide group form metal chelates with only two isomers. Due to the presence of D03A chelating unit, macrocyclic chelants containing a
10 succinimide or phthalimide group will form lanthanide metal chelates with high thermodynamic stability and kinetic inertness.

The present invention also provides macrocyclic chelants containing a linker group, such as phospho-
15 triester, phosphodiester, phosphodiestermonoamide-, and phosphomonoester-diamide. Like carbonyl-O and carboxylate-O atoms, the phosphonyl-O and phosphonate-O are also good donor atoms for "hard" trivalent lanthanide metal ions. These macrocyclic chelants form
20 either neutral or anionic metal chelates with trivalent metal ions such as In^{3+} , Y^{3+} , Sm^{3+} , Gd^{3+} , Dy^{3+} , Ho^{3+} , Yb^{3+} , and Lu^{3+} .

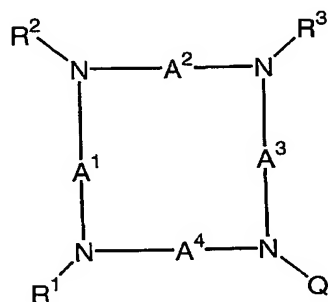
DETAILED DESCRIPTION OF THE INVENTION

25 The present invention provides macrocyclic chelants that can rapidly form highly stable metal chelates useful as diagnostic or therapeutic metalloradiopharmaceuticals, or magnetic resonance imaging contrast agents, or X-ray or CT contrast agents.
30 The macrocyclic chelants can also serve as bifunctional chelators (BFCs) for attaching metal ions to bio-directing groups including proteins, peptides,

peptidomimetics, and non-peptides that bind in vivo to a receptor or enzyme that is expressed or up-regulated at a site or in a disease state. The target specific metallopharmaceuticals of the present invention are
 5 useful in the diagnosis of disease by MRI, X-ray, CT imaging or scintigraphy or in the treatment of disease by systemic radiotherapy.

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula:

10



or pharmaceutically acceptable salts thereof,

wherein:

R¹, R², and R³ are independently selected from: C₁-C₁₀
 15 alkyl substituted with 1-5 R⁴, C₁-C₁₀ fluoroalkyl substituted with 1-5 R⁴, C₂-C₁₀ alkenyl substituted with 1-5 R⁴, C₂-C₁₀ fluoroalkenyl substituted with 1-5 R⁴, and aryl substituted with 1-5 R⁴, fluoroaryl substituted with 1-5 R⁴;

20 R⁴ is independently selected at each occurrence from: C(=O)R⁵, S(O)₂OR⁵, C(=O)OR⁵, C(=O)NR⁶R⁷, PO(OR⁶)(OR⁷);

R⁵, R⁶ and R⁷ are independently selected from: H, C₁-C₁₀ alkyl substituted with 0-5 R⁸, C₂-C₁₀ alkenyl substituted with 0-5 R⁸, C₃-C₁₀ cycloalkyl substituted with 0-5 R⁸,

C₁-C₁₀ fluoroalkyl substituted with 0-5 R⁸, C₂-C₁₀ fluoroalkenyl substituted with 0-5 R⁸, aryl substituted with 0-5 R⁸, and fluoroaryl substituted with 0-3 R⁸, said C₁-C₁₀ alkyl and C₂-C₁₀ alkenyl groups optionally
 5 interrupted with -O-, -S-, -NH-, -S(O)-, -S(O)₂-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, or -NHC(S)NH-;

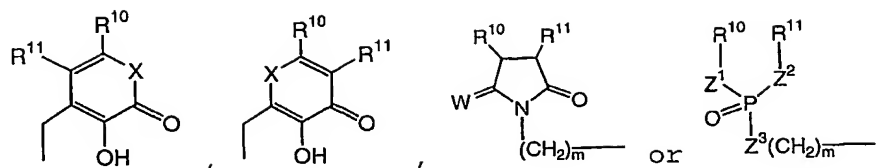
or alternatively, R⁶ and R⁷ may be taken together, with the atoms through which they are attached, to form a C₃-
 10 C₁₀ cycloalkyl substituted with 0-5 R⁸, C₃-C₁₀ cycloalkenyl substituted with 0-5 R⁸, aryl substituted with 0-5 R⁸, or fluoroaryl substituted with 0-5 R⁸; said C₃-C₁₀ alkyl and C₃-C₁₀ cycloalkenyl groups optionally interrupted with -O-, -S-, -NR⁹-, -S(O)-, -S(O)₂-, -
 15 P(O)(OR⁹)-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, or -NHC(S)NH-;

R⁸ is independently selected at each occurrence from: H, -OH, -NHR⁹, -C(=O)R⁹, -OC(=O)R⁹, -OC(=O)OR⁹, -C(=O)OR⁹, -C(=O)N(R⁹)₂, -PO(OR⁹)₂, -SR⁹, -SOR⁹, -SO₂R⁹, -NHC(=O)R⁹, -
 20 NHC(=O)NHR⁹, -CH₂OR⁹, and -NHC(=S)NHR⁹;

R⁹ is independently selected at each occurrence from: H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkyl, C₁-C₆ alkenyl, C₃-C₆ cycloalkenyl, C₁-C₆ fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

25 A¹, A², A³, and A⁴ are independently -(CR⁵R⁵)_n-, wherein n is 2 or 3.

Q is a functional group selected from:



- wherein R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^{12} , and aryl substituted with 0-5 R^{12} ,
- or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;
- m is 1-3;
- W is selected from two hydrogen atoms or O;
- R^{12} is independently selected at each occurrence from the group: COR^{13} , $C(=O)OR^{13}$, $C(=O)N(R^{13})_2$, $PO(OR^{13})_2$, OR^{13} , and SO_2OR^{13} ;
- R^{13} is independently selected at each occurrence from the group: H, and C_1 - C_6 alkyl;
- X is selected from O or NR^5 ; and
- Z^1 , Z^2 , and Z^3 are independently selected from: O, NH , CH_2NH , and a direct bond.

- [2] A preferred embodiment of the present invention is a compound of embodiment [1], wherein:

- R^1 , R^2 , and R^3 are independently selected from: C_1 - C_3 alkyl substituted with 1-2 R^4 , C_1 - C_3 fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;
- 5 R^5 , R^6 and R^7 are independently selected from: H, C_1 - C_3 alkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_1 - C_3 fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;
- or alternatively, R^6 and R^7 may be taken together, with
10 the atoms through which they are attached, to form a C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkenyl substituted with 0-2 R^8 , or an aryl substituted with 0-2 R^8 ;
- R^9 is independently selected at each occurrence from: H,
15 C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;
- A^1 , A^2 , A^3 , and A^4 are $-(CR^5R^5)_2-$;
- R^{10} and R^{11} are independently selected at each occurrence
20 from: H, C_1 - C_3 alkyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkyl substituted with 0-2 R^{12} , C_1 - C_3 fluoroalkyl substituted with 0-2 R^{12} , C_2 - C_3 alkenyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkenyl substituted with 0-2 R^{12} , C_2 - C_3 fluoroalkenyl substituted with 0-2 R^{12} , and aryl
25 substituted with 0-2 R^{12} ;
- or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl group substituted with 0-2 R^{12} , or aryl group substituted with 0-2 R^{12} ;
- 30 R^{13} is H or C_1 - C_3 alkyl; and

Z^1 , Z^2 , and Z^3 are independently selected from: O, NH, and a direct bond.

[3] A more preferred embodiment of the present invention is a compound of embodiment [1] or [2],

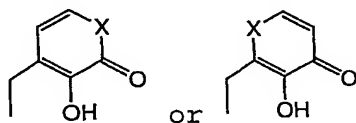
5 wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , and A^3 are $-(\text{CH}_2)_2-$; and

10 Q is a functional group of the formula:



[4] Another more preferred embodiment of the present invention is a compound of embodiment [2],

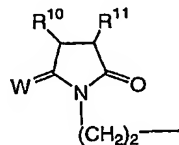
15 wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 and A^4 are $-(\text{CH}_2)_2-$; and

20 Q is a functional group of the formula:



wherein R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

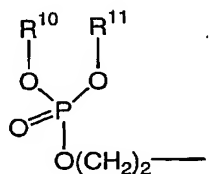
[5] Another more preferred embodiment of the present invention is a compound of embodiment [2],
5 wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

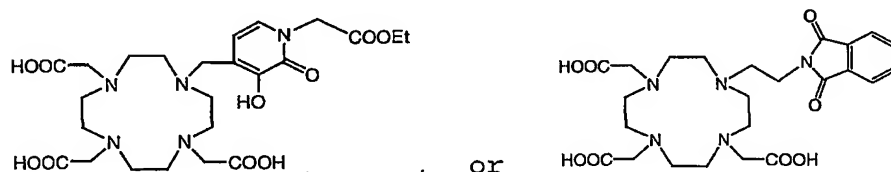
R^4 is independently elected at each occurrence from:
 COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

10 Q is a functional group of the formula:



[6] A further preferred embodiment of the present invention is a compound of embodiment [2] of the
15 formula:

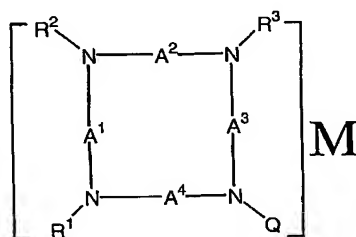


[7] In a second embodiment, the present invention provides a novel metal chelate complex comprising a
20 compound according to any one of embodiments [1]-[6] complexed to a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

[8] In another embodiment, the present invention provides a novel metal chelate complex comprising a compound according to any one of embodiments [1]-[6] complexed to a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re .

[9] In another embodiment, the present invention provides a metal chelate complex according to embodiment [7] or [8] of the formula:

10



or pharmaceutically acceptable salts thereof,

wherein:

15 M is X or X^1 ;

wherein:

X is a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re ;

20 X^1 is a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90;

wherein:

R^1 , R^2 , and R^3 are independently selected from: $\text{C}_1\text{-C}_{10}$ alkyl substituted with 1-5 R^4 , $\text{C}_1\text{-C}_{10}$ fluoroalkyl substituted with 1-5 R^4 , $\text{C}_2\text{-C}_{10}$ alkenyl substituted with

1-5 R^4 , C_2 - C_{10} fluoroalkenyl substituted with 1-5 R^4 , and aryl substituted with 1-5 R^4 , fluoroaryl substituted with 1-5 R^4 ;

- R^4 is independently selected at each occurrence from: -
 5 $C(=O)R^5$, $-S(O)_2OR^5$, $-C(=O)OR^5$, $-C(=O)NR^6R^7$, $-PO(OR^6)(OR^7)$;
 R^5 , R^6 and R^7 are independently selected from: H, C_1 - C_{10} alkyl substituted with 0-5 R^8 , C_2 - C_{10} alkenyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^8 , C_2 - C_{10}
 10 fluoroalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , and fluoroaryl substituted with 0-3 R^8 , said C_1 - C_{10} alkyl and C_2 - C_{10} alkenyl groups optionally interrupted with -O-, -S-, -NH-, -S(O)-, -S(O)₂-, -
 $P(O)(OR^9)O-$, $-P(O)(NHR^9)O-$, $-C(O)NH-$, $-NHC(O)-$, -
 15 $NHC(O)NH-$, $-NHC(S)NH-$;

- or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^8 , aryl substituted
 20 with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally interrupted with -O-, -S-, -NR⁹-, -S(O)-, -S(O)₂-, -
 $P(O)(OR^9)-$, $-P(O)(OR^9)O-$, $-P(O)(NHR^9)-$, $-P(O)(NHR^9)O-$, -
 $C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, or $-NHC(S)NH-$;

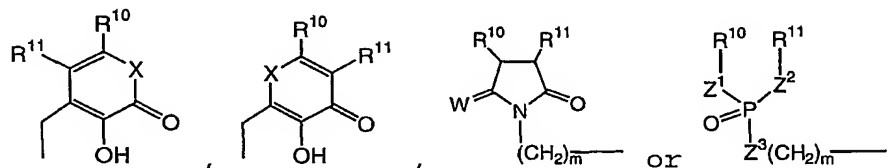
- 25 R^8 is independently selected at each occurrence from: H, OH, NHR^9 , $C(=O)R^9$, $OC(=O)R^9$, $OC(=O)OR^9$, $C(=O)OR^9$, $C(=O)N(R^9)_2$, $PO(OR^9)_2$, SR^9 , SOR^9 , SO_2R^9 , $NHC(=O)R^9$, $NHC(=O)NHR^9$, CH_2OR^9 , and $NHC(=S)NHR^9$;

- R^9 is independently selected at each occurrence from: H,
 30 C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6

alkenyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

A¹, A², A³, and A⁴ are independently -(CR⁵R⁵)_n-, wherein n is 2 or 3.

5 Q is a functional group selected from:



wherein R¹⁰ and R¹¹ are independently selected at each
 10 occurrence from: H, C₁-C₁₀ alkyl substituted with 0-5
 R¹², C₃-C₁₀ cycloalkyl substituted with 0-5 R¹², C₁-C₁₀
 fluoroalkyl substituted with 0-5 R¹², C₂-C₁₀ alkenyl
 substituted with 0-5 R¹², C₃-C₁₀ cycloalkenyl substituted
 with 0-5 R¹², C₂-C₁₀ fluoroalkenyl substituted with 0-5
 15 R¹², and aryl substituted with 0-5 R¹²,

or, alternatively, R¹⁰ and R¹¹ may be taken together,
 with the atoms through which they are attached, to form
 a cyclic ring system, said ring system selected from:
 C₃-C₁₀ cycloalkyl substituted with 0-5 R¹², and aryl
 20 substituted with 0-3 R¹²;

m is 1-3;

W is selected from two hydrogen atoms or O;

R¹² is independently selected at each occurrence from
 the group: -COR¹³, -C(=O)OR¹³, -C(=O)N(R¹³)₂, -PO(OR¹³)₂, -
 25 OR¹³, and -SO₂OR¹³;

R¹³ is independently selected at each occurrence from the group: H, and C₁-C₆ alkyl;

X is selected from -O- or -NR⁵-; and

Z¹, Z², and Z³ are independently selected from: -O-, -NH-
5 ; -CH₂NH-, and a direct bond.

[10] Another preferred embodiment of the present invention is a metal chelate complex of embodiment [9], wherein:

R¹, R², and R³ are independently selected from: C₁-C₃
10 alkyl substituted with 1-2 R⁴, C₁-C₃ fluoroalkyl substituted with 1-2 R⁴, aryl substituted with 1-2 R⁴, and fluoroaryl substituted with 1-2 R⁴;

R⁵, R⁶ and R⁷ are independently selected from: H, C₁-C₃
15 alkyl substituted with 0-2 R⁸, C₃-C₆ cycloalkyl substituted with 0-2 R⁸, C₁-C₃ fluoroalkyl substituted with 0-2 R⁸, and aryl substituted with 0-2 R⁸;

or alternatively, R⁶ and R⁷ may be taken together, with the atoms through which they are attached, to form a C₃-C₆ cycloalkyl substituted with 0-2 R⁸, C₃-C₆ cycloalkenyl
20 substituted with 0-2 R⁸, or an aryl substituted with 0-2 R⁸;

R⁹ is independently selected at each occurrence from: H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkyl, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkenyl, benzyl,
25 fluorobenzyl, phenyl, and fluorophenyl;

A¹, A², A³, and A⁴ are -(CR⁵R⁵)₂-;

R¹⁰ and R¹¹ are independently selected at each occurrence from: H, C₁-C₃ alkyl substituted with 0-2 R¹², C₃-C₆ cycloalkyl substituted with 0-2 R¹², C₁-C₃ fluoroalkyl
30 substituted with 0-2 R¹², C₂-C₃ alkenyl substituted with

0-2 R^{12} , C_3 - C_6 cycloalkenyl substituted with 0-2 R^{12} , C_2 - C_3 fluoroalkenyl substituted with 0-2 R^{12} , and aryl substituted with 0-2 R^{12} ,

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl group substituted with 0-2 R^{12} , or aryl group substituted with 0-2 R^{12} ;

R^{13} is H or C_1 - C_3 alkyl; and

Z^1 , Z^2 , and Z^3 are independently selected from: O, NH, and a direct bond.

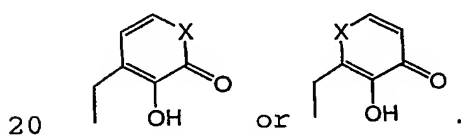
[11] Another more preferred embodiment of the present invention is a metal chelate complex of embodiment [10], wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: $-\text{COOH}$, $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:



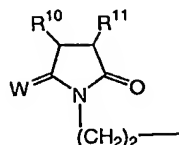
[12] Another more preferred embodiment of the present invention is a metal chelate complex of embodiment [10], wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: $-\text{COOH}$, $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(CH_2)_2-$; and

Q is a functional group of the formula:



- 5 wherein R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

[13] Another more preferred embodiment of the present invention is a metal chelate complex of embodiment [10], wherein:

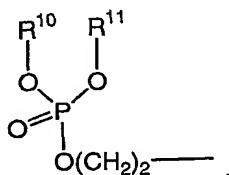
- 10 R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from:
 $COOH$, PO_3H_2 , SO_3H , and $C(=O)NR^6R^7$;

A^1 , A^2 , A^3 , and A^4 are $-(CH_2)_2-$; and

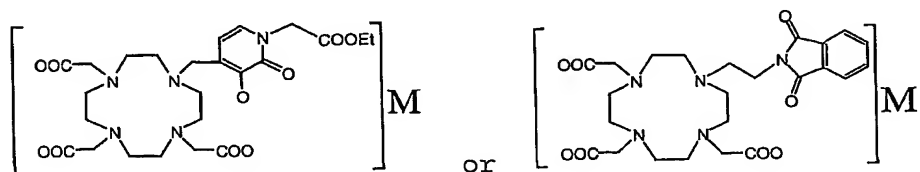
Q is a functional group of the formula:

15

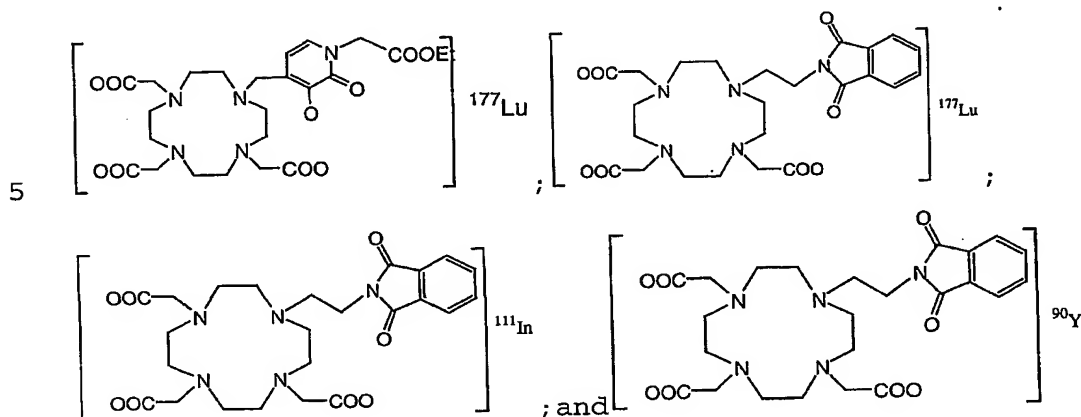


[14] Another further preferred embodiment of the present invention is a metal chelate complex of embodiment [10] that is:

20



[15] Another further preferred embodiment of the present invention is a metal chelate complex of embodiment [10] selected from the group consisting of:



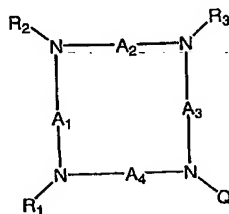
[16] A third embodiment of the present invention is a novel conjugate of the formula:



or pharmaceutically acceptable salts thereof,

wherein,

C_h is a chelator of formula:



15

wherein:

R^1 , R^2 , and R^3 are independently selected from: C_1 - C_{10} alkyl substituted with 1-5 R^4 , C_1 - C_{10} fluoroalkyl substituted with 1-5 R^4 , C_2 - C_{10} alkenyl substituted with 1-5 R^4 , C_2 - C_{10} fluoroalkenyl substituted with 1-5 R^4 , and aryl substituted with 1-5 R^4 , fluoroaryl substituted with 1-5 R^4 ;

R^4 is independently selected at each occurrence from:
 10 $C(=O)R^5$, $S(O)_2OR^5$, $C(=O)OR^5$, $C(=O)NR^6R^7$, $PO(OR^6)(OR^7)$;

R^5 , R^6 and R^7 are independently selected from: H, a direct bond to L_n , C_1 - C_{10} alkyl substituted with 0-5 R^8 , C_2 - C_{10} alkenyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^8 , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , and fluoroaryl substituted with 0-3 R^8 , said C_1 - C_{10} alkyl and C_2 - C_{10} alkenyl groups optionally interrupted with O, S, NH, $S(O)$, $S(O)_2$, $P(O)(OR^9)O$, $P(O)(NHR^9)O$, $C(O)NH$, $NHC(O)$,
 20 $NHC(O)NH$, $NHC(S)NH$;

or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally interrupted with -O-, -S-, - NR^9 -, - $S(O)$ -, - $S(O)_2$ -, - $P(O)(OR^9)$ -, - $P(O)(OR^9)O$ -, - $P(O)(NHR^9)$ -, - $P(O)(NHR^9)O$ -, - $C(O)NH$ -, - $NHC(O)$ -, - $NHC(O)NH$ -, or - $NHC(S)NH$ -;

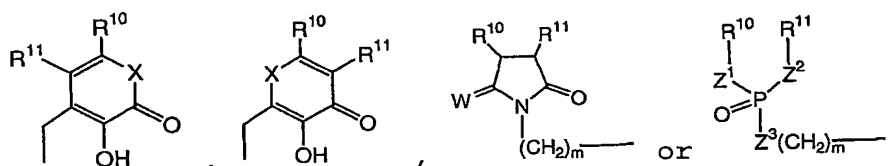
30 R^8 is independently selected at each occurrence from: -H, -OH, - NHR^9 , - $C(=O)R^9$, - $OC(=O)R^9$, - $OC(=O)OR^9$, -

$C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-PO(OR^9)_2$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $--NHC(=O)R^9$, $NHC(=O)NHR^9$, $-CH_2OR^9$, $-NHC(=S)NHR^9$, and a direct bond to L_n ;

R^9 is independently selected at each occurrence from: H,
 5 C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 fluoroalkyl, C_1-C_6 alkenyl, C_3-C_6 cycloalkenyl, C_1-C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, fluorophenyl, and a direct bond to L_n ;

A^1 , A^2 , A^3 , and A^4 are independently $-(CR^5R^5)_n-$, wherein n
 10 is 2 or 3.

Q is a functional group selected from:



15 wherein:

R^{10} and R^{11} are independently selected at each occurrence from: H, C_1-C_{10} alkyl substituted with 0-5 R^{12} , C_3-C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1-C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2-C_{10} alkenyl substituted with 0-5 R^{12} , C_3-C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2-C_{10} fluoroalkenyl substituted with 0-5 R^{12} , aryl substituted with 0-5 R^{12} , and a direct bond to L_n ;

20

or, alternatively, R^{10} and R^{11} may be taken together with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3-C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

25

m is 1-3;

W is selected from two hydrogen atoms or O;

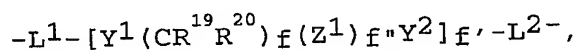
R¹² is independently selected at each occurrence from the group: -COR¹³, -C(=O)OR¹³, -C(=O)N(R¹³)₂, -PO(OR¹³)₂, -OR¹³, -SO₂OR¹³, and a direct bond to L_n;

R¹³ is independently selected at each occurrence from the group: H, C₁-C₆ alkyl, and a direct bond to L_n;

X is selected from O or NR⁵;

Z¹, Z², and Z³ are independently selected at each occurrence from: O, NH, CH₂NH, and a direct bond;

L_n is a linking group of formula:



L¹ is -[(CH₂)_gZ¹]_{g'}-(CR¹⁹R²⁰)_{g''}-;

L² is -(CR¹⁹R²⁰)_{g''}-[Z¹(CH₂)_g]_{g'}-;

g is independently 0-10;

g' is independently 0-1;

g'' is independently 0-10;

f is independently 0-10;

f' is independently 0-10;

f'' is independently 0-1;

Y¹ and Y² are independently selected, at each occurrence, from: a direct bond, -O-, -NR²⁰-, -C(=O)-, -C(=O)O-, -OC(=O)O-, -C(=O)NH-, -C(=NR²⁰)-, -S-, -S(O)-, -S(O)₂-, -NHC(=O)-, -(NH)₂C(=O)-, and -(NH)₂C(=S)-;

R^{19} and R^{20} are independently selected at each occurrence from: H, a direct bond to BM, C₁-C₁₀ alkyl substituted with 0-5 R^{21} , and alkaryl wherein the aryl is substituted with 0-5 R^{21} ;

- 5 - R^{21} is independently selected at each occurrence from the group: $-NHR^{22}$, $-C(=O)R^{22}$, $-OC(=O)R^{22}$, $-OC(=O)OR^{22}$, $-C(=O)OR^{22}$, $-C(=O)NR_2^{22}$, $-CN$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-NHC(=O)R^{22}$, $-NHC(=O)NHR^{22}$, $-NHC(=S)NHR^{22}$, and a direct bond to BM;
- 10 R^{22} is independently selected at each occurrence from the group: H, C₁-C₆ alkyl, benzyl, phenyl, and a direct bond to BM; and
- BM is a biologically active targeting molecule selected from the group: IIb/IIIa receptor ligands, fibrin
- 15 binding peptides, leukocyte binding peptides, chemotactic peptides, LTB₄ receptor antagonists, somatostatin analogs, selectin binding peptides, vitronectin receptor antagonists, growth factor receptor antagonists, tyrosine kinase inhibitors; matrix
- 20 metalloproteinase inhibitors, oligonucleotides, fatty acids, nitroimidazoles, and carbohydrates.

[17] Another preferred embodiment of the present invention is a conjugate of embodiment [16], wherein, R^1 , R^2 , and R^3 are independently selected from: C₁-C₃

25 alkyl substituted with 1-2 R^4 , C₁-C₃ fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;

R^5 , R^6 and R^7 are independently selected from: H, a direct bond to L_n, C₁-C₃ alkyl substituted with 0-2 R^8 ,

30 C₃-C₆ cycloalkyl substituted with 0-2 R^8 , C₁-C₃

fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;

or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C₃-C₆ cycloalkyl substituted with 0-2 R^8 , C₃-C₆ cycloalkenyl substituted with 0-2 R^8 , or aryl substituted with 0-2 R^8 ;

R^9 is independently selected at each occurrence from: H, a direct bond to L_n , C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkyl, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

A^1 , A^2 , A^3 , and A^4 are $-(CR^5R^5)_2-$;

R^{10} and R^{11} are independently selected at each occurrence from: H, a direct bond to L_n , C₁-C₃ alkyl substituted with 0-2 R^{12} , C₃-C₆ cycloalkyl substituted with 0-2 R^{12} , C₁-C₃ fluoroalkyl substituted with 0-2 R^{12} , C₂-C₃ alkenyl substituted with 0-2 R^{12} , C₃-C₆ cycloalkenyl substituted with 0-2 R^{12} , C₂-C₃ fluoroalkenyl substituted with 0-2 R^{12} , and aryl substituted with 0-2 R^{12} ,

or, alternatively, R^{10} and R^{11} may be taken together to form a C₃-C₁₀ cycloalkyl group substituted with 0-2 R^{12} , or ortho-aryl group substituted with 0-2 R^{12} ;

R^{13} is H or C₁-C₃ alkyl; and

Z^1 , Z^2 , and Z^3 are independently selected from: O, NH, and a direct bond.

[18] Another more preferred embodiment of the present invention is a conjugate of embodiment [17], wherein:

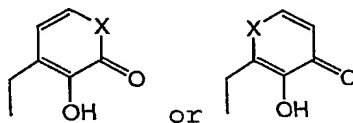
R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from: -
COOH, $-PO_3H_2$, $-SO_3H$, and $-C(=O)NR^6R^7$;

A^1 , A^2 , A^3 , and A^4 are $-(CH_2)_2-$; and

Q is a functional group of the formula:

5



[19] Another more preferred embodiment of the present invention is a conjugate of embodiment [17], wherein:

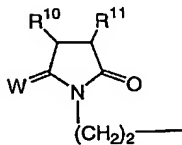
10 R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from:
COOH, PO_3H_2 , SO_3H , and $C(=O)NR^6R^7$;

A^1 , A^2 , A^3 and A^4 are $-(CH_2)_2-$; and

Q is a functional group of the formula:

15



wherein:

R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

20 [20] Another more preferred embodiment of the present invention is a conjugate of embodiment [17], wherein:

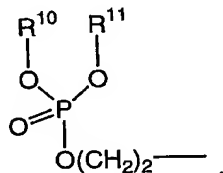
R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from: -
COOH, $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:

5

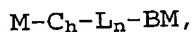


[21] A fourth embodiment of the present invention is a novel metallopharmaceutical comprising a conjugate according to embodiment [16] chelated with a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re .

[22] A fourth embodiment of the present invention is a novel metallopharmaceutical comprising a conjugate according to embodiment [16] chelated with a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

[23] A fourth embodiment of the present invention is a novel metallopharmaceutical according to embodiment [21] or [22] of the formula:

20



or pharmaceutically acceptable salts thereof,

wherein:

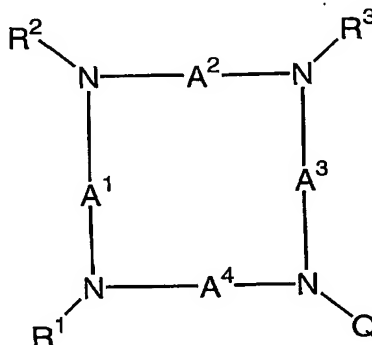
M is X or X^1 ;

wherein:

X is a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re ;

X^1 is a metal ion of atomic number 21-31, 39-49, 50, 56-
5 80, 82, 83, 90;

C_h is a chelator of formula:



wherein:

R^1 , R^2 , and R^3 are independently selected from: $\text{C}_1\text{-C}_{10}$
10 alkyl substituted with 1-5 R^4 , $\text{C}_1\text{-C}_{10}$ fluoroalkyl
substituted with 1-5 R^4 , $\text{C}_2\text{-C}_{10}$ alkenyl substituted with
1-5 R^4 , $\text{C}_2\text{-C}_{10}$ fluoroalkenyl substituted with 1-5 R^4 , and
aryl substituted with 1-5 R^4 , fluoroaryl substituted
with 1-5 R^4 ;

15 R^4 is independently selected at each occurrence from:
 $\text{C}(=\text{O})\text{R}^5$, $\text{S}(\text{O})_2\text{OR}^5$, $\text{C}(=\text{O})\text{OR}^5$, $\text{C}(=\text{O})\text{NR}^6\text{R}^7$, $\text{PO}(\text{OR}^6)(\text{OR}^7)$;

R^5 , R^6 and R^7 are independently selected from: H, a
direct bond to L_n , $\text{C}_1\text{-C}_{10}$ alkyl substituted with 0-5 R^8 ,
 $\text{C}_2\text{-C}_{10}$ alkenyl substituted with 0-5 R^8 , $\text{C}_3\text{-C}_{10}$ cycloalkyl
20 substituted with 0-5 R^8 , $\text{C}_1\text{-C}_{10}$ fluoroalkyl substituted
with 0-5 R^8 , $\text{C}_2\text{-C}_{10}$ fluoroalkenyl substituted with 0-5
 R^8 , aryl substituted with 0-5 R^8 , and fluoroaryl
substituted with 0-3 R^8 , said $\text{C}_1\text{-C}_{10}$ alkyl and $\text{C}_2\text{-C}_{10}$
alkenyl groups optionally interrupted with -O-, -S-, -

NH-, -S(O)-, -S(O)₂-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)O-, -
C(O)NH-, -NHC(O)-, -NHC(O)NH-, -NHC(S)NH-;

- or alternatively, R⁶ and R⁷ may be taken together, with
the atoms through which they are attached, to form a C₃-
5 C₁₀ cycloalkyl substituted with 0-5 R⁸, C₃-C₁₀
cycloalkenyl substituted with 0-5 R⁸, aryl substituted
with 0-5 R⁸, or fluoroaryl substituted with 0-5 R⁸; said
C₃-C₁₀ alkyl and C₃-C₁₀ cycloalkenyl groups optionally
interrupted with O, S, NR⁹, S(O), S(O)₂, P(O)(OR⁹),
10 P(O)(OR⁹)O, P(O)(NHR⁹), P(O)(NHR⁹)O, C(O)NH, NHC(O),
NHC(O)NH, NHC(S)NH;

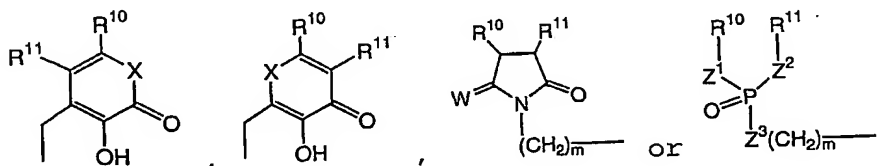
- R⁸ is independently selected at each occurrence from: H,
OH, NHR⁹, C(=O)R⁹, OC(=O)R⁹, OC(=O)OR⁹, C(=O)OR⁹,
C(=O)N(R⁹)₂, PO(OR⁹)₂, SR⁹, SOR⁹, SO₂R⁹, NHC(=O)R⁹,
15 NHC(=O)NHR⁹, CH₂OR⁹, NHC(=S)NHR⁹, and a direct bond to
L_n;

- R⁹ is independently selected at each occurrence from: H,
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkyl, C₁-C₆
alkenyl, C₃-C₆ cycloalkenyl, C₁-C₆ fluoroalkenyl, benzyl,
20 fluorobenzyl, phenyl, fluorophenyl, and a direct bond to
L_n;

A¹, A², A³, and A⁴ are independently -(CR⁵R⁵)_n-, wherein n
is 2 or 3.

Q is a functional group selected from:

25



wherein:

R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^{12} , aryl substituted with 0-5 R^{12} , and a direct bond to L_n ;

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

m is 1-3;

W is selected from two hydrogen atoms or O;

R^{12} is independently selected at each occurrence from the group: COR^{13} , $C(=O)OR^{13}$, $C(=O)N(R^{13})_2$, $PO(OR^{13})_2$, OR^{13} , SO_2OR^{13} , and a direct bond to L_n ;

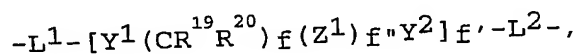
R^{13} is independently selected at each occurrence from the group: H, C_1 - C_6 alkyl, and a direct bond to L_n ;

X is selected from O or NR^5 ;

Z^1 , Z^2 , and Z^3 are independently selected at each occurrence from: O, NH , CH_2NH , and a direct bond;

L_n is a linking group of formula:

25



L^1 is $-[(CH_2)_g Z^1]_g-(CR^{19}R^{20})_g-$;

L^2 is $-(CR^{19}R^{20})_g-[Z^1(CH_2)_g]_{g'}-$;

g is independently 0-10;

g' is independently 0-1;

g'' is independently 0-10;

5 f is independently 0-10;

f' is independently 0-10;

f'' is independently 0-1;

Y^1 and Y^2 are independently selected at each occurrence from: a direct bond, $-O-$, $-NR^{20}-$, $-C=O-$, $-C(=O)O-$, $-OC(=O)O-$, $-C(=O)NH-$, $-C(=NR^{20})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-NHC(=O)-$, $-(NH)_2C(=O)-$, and $-(NH)_2(C=S)-$;

R^{19} and R^{20} are independently selected at each occurrence from: H, a direct bond to BM, C_1 - C_{10} alkyl substituted with 0-5 R^{21} , and alkaryl wherein the aryl is substituted with 0-5 R^{21} ;

R^{21} is independently selected at each occurrence from the group: $-NHR^{22}$, $-C(=O)R^{22}$, $-OC(=O)R^{22}$, $-OC(=O)OR^{22}$, $-C(=O)OR^{22}$, $-C(=O)NR^{22}$, $-CN$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-NHC(=O)R^{22}$, $-NHC(=O)NHR^{22}$, $-NHC(=S)NHR^{22}$, and a direct bond to BM;

R^{22} is independently selected at each occurrence from the group: H, C_1 - C_6 alkyl, benzyl, phenyl, and a direct bond to BM; and

BM is a biologically active targeting molecule selected from the group: IIb/IIIa receptor ligands, fibrin binding peptides, leukocyte binding peptides, chemotactic peptides, LTB_4 receptor antagonists,

somatostatin analogs, selectin binding peptides, vitronectin receptor antagonists, growth factor receptor antagonists, tyrosine kinase inhibitors, matrix metalloproteinase inhibitors, oligonucleotides, fatty acids, nitroimidazoles, and carbohydrates.

[24] Another preferred embodiment of the present invention is a metallopharmaceutical of embodiment [23], wherein,

R^1 , R^2 , and R^3 are independently selected from: C_1 - C_3 alkyl substituted with 1-2 R^4 , C_1 - C_3 fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;

R^5 , R^6 and R^7 are independently selected from: H, a direct bond to L_n , C_1 - C_3 alkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_1 - C_3 fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;

or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkenyl substituted with 0-2 R^8 , or aryl substituted with 0-2 R^8 ;

R^9 is independently selected at each occurrence from: H, a direct bond to L_n , C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

A^1 , A^2 , A^3 , and A^4 are $-(CR^5R^5)_2-$;

R^{10} and R^{11} are independently selected at each occurrence from: H, a direct bond to L_n , C_1 - C_3 alkyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkyl substituted with 0-2 R^{12} ,

C₁-C₃ fluoroalkyl substituted with 0-2 R¹², C₂-C₃ alkenyl substituted with 0-2 R¹², C₃-C₆ cycloalkenyl substituted with 0-2 R¹², C₂-C₃ fluoroalkenyl substituted with 0-2 R¹², and aryl substituted with 0-2 R¹²,

- 5 or, alternatively, R¹⁰ and R¹¹ may be taken together, with the atoms through which they are attached, to form a C₃-C₁₀ cycloalkyl group substituted with 0-2 R¹², or ortho-aryl group substituted with 0-2 R¹²;

R¹³ is H or C₁-C₃ alkyl; and

- 10 Z¹, Z², and Z³ are independently selected from: O, NH, and a direct bond.

[25] Another more preferred embodiment of the present invention is a metallopharmaceutical of embodiment [24], wherein:

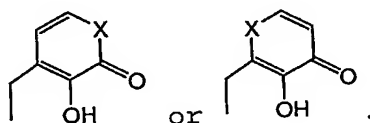
- 15 R¹, R², and R³ are -CH₂R⁴;

R⁴ is independently elected at each occurrence from: -COOH, -PO₃H₂, -SO₃H, and -C(=O)NR⁶R⁷;

A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:

20



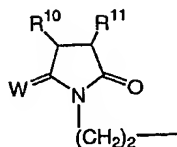
[26] Another more preferred embodiment of the present invention is a metallopharmaceutical of embodiment [24], wherein:

- 25 R¹, R², and R³ are -CH₂R⁴;

R⁴ is independently elected at each occurrence from: -COOH, -PO₃H₂, -SO₃H, and -C(=O)NR⁶R⁷;

A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:



- 5 wherein R¹⁰ and R¹¹ are taken together to form a phenyl group substituted with 0-2 R¹².

[27] Another more preferred embodiment of the present invention is a metallopharmaceutical of embodiment [24], wherein:

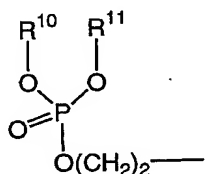
- 10 R¹, R², and R³ are -CH₂R⁴;

R⁴ is independently elected at each occurrence from:
COOH, PO₃H₂, SO₃H, and C(=O)NR⁶R⁷;

A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:

15



- [28] Another preferred embodiment of the present invention is a radiopharmaceutical composition comprising a metallopharmaceutical of embodiment [21] and a pharmaceutically acceptable carrier.
- 20

[29] Another preferred embodiment of the present invention is a method of treating cancer in a patient comprising administering to a patient in need thereof a

therapeutically effective amount of a radiopharmaceutical composition according to embodiment [28], wherein BM is a biologically active targeting molecule selected from the group: vitronectin receptor antagonists, growth factor receptor antagonists, matrix metalloproteinase inhibitors and tyrosine kinase inhibitors.

[30] Another preferred embodiment of the present invention is a method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- (ii) generating a radioimage of at least a part of said patient's body;

wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and
M is ^{62}Cu , ^{60}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, or ^{111}In .

[31] Another preferred embodiment of the present invention is a method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- (ii) generating a MRI image of at least a part of said patient's body;

wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and
M is paramagnetic metal ion of atomic number 21-29, 42-44 or 58-70.

[32] Another preferred embodiment of the present invention is a method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- (ii) generating an X-ray or CT image of at least a part of said patient's body;
- 5 wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and

M is heavy metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

- 10 [33] Another preferred embodiment of the present invention is a method of diagnosing infection, inflammation or transplant rejection in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- 15 (ii) generating a radioimage of at least a part of said patient's body;

wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a LTB₄ receptor antagonist; and

20

M is ⁶²Cu, ⁶⁰Cu, ⁶⁷Ga, ⁶⁸Ga, ^{99m}Tc, or ¹¹¹In.

- [34] Another preferred embodiment of the present invention is a method of diagnosing infection, inflammation or transplant rejection in a patient,
- 25 comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- 30 (ii) generating a MRI image of at least a part of said patient's body;

wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a LTB₄ receptor antagonist; and

M is paramagnetic metal ion of atomic number 21-29, 42-
5 44 or 58-70.

[35] Another preferred embodiment of the present invention is a method of diagnosing infection, inflammation or transplant rejection in a patient, comprising:

- 10 (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
 (ii) generating an X-ray or CT image of at least a part of said patient's body;

15 wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a LTB₄ receptor antagonist; and

M is heavy metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

20 [36] Another preferred embodiment of the present invention is a method of detecting new angiogenic vasculature in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical
25 according to embodiment [23]; and
 (ii) generating a radioimage of at least a part of said patient's body;

wherein BM is a vitronectin receptor antagonist, a somatostatin analog, or a growth factor receptor
30 antagonist; and

M is ⁶²Cu, ⁶⁰Cu, ⁶⁷Ga, ⁶⁸Ga, ^{99m}Tc, or ¹¹¹In.

[37] Another preferred embodiment of the present invention is a method of detecting new angiogenic vasculature in a patient, comprising:

- 5 (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- (ii) generating a MRI image of at least a part of said patient's body;

wherein BM is a vitronectin receptor antagonist, a
10 somatostatin analog, or a growth factor receptor antagonist; and
M is paramagnetic metal ion of atomic number 21-29, 42-44 or 58-70.

[38] Another preferred embodiment of the present
15 invention is a method of detecting new angiogenic vasculature in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical according to embodiment [23]; and
- 20 (ii) generating an X-ray or CT image of at least a part of said patient's body;

wherein BM is a vitronectin receptor antagonist, a somatostatin analog, or a growth factor receptor antagonist; and
25 M is heavy metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

[39] Another preferred embodiment of the present invention is a method of metal detoxification in a patient comprising administering to a patient in need
30 thereof a detoxifying amount of a compound according to embodiment [1], or a weak chelate complex or salt form thereof, with a pharmaceutically acceptable counterion.

[40] Another preferred embodiment of the present invention is a kit for preparing a metallopharmaceutical composition, comprising the following ingredients:

- (i) a conjugate of embodiment [16];
- 5 (ii) a pharmaceutically acceptable carrier, a formulating agent, or an adjuvant;
- (iii) a solution of a salt of a metal, or chelate of a metal; and
- 10 (iv) instructions for reacting the ingredients present in the kit;

wherein the metal is selected from the group consisting of a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, or 90.

[41] Another preferred embodiment of the present invention is a kit for forming a radiopharmaceutical complex comprising the following components:

- (i) a conjugate of embodiment [16];
- (ii) optionally a reducing agent; and
- 20 (iii) instructions for reacting the components of said kit with a radionuclide solution.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

DEFINITIONS

The term "direct bond" as used herein, means a chemical bond.

The term "substituted," as used herein, means that
5 any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O),
10 then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double
15 bond be part (i.e., within) of the ring.

The term "alkyl", as used herein, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not
20 limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl.

The term "alkaryl", mean an -arylalkyl group wherein the aryl and alkyl are as herein described. Examples of arylalkyl include, but are not limited to, -
25 phenylmethyl, -phenylethyl, -phenylpropyl, -phenylbutyl, and -phenylpentyl.

The term "haloalkyl", as used herein, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number
30 of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$).

Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

The term "alkoxy", as used herein, represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo, and s-pentoxo.

The term "cycloalkyl" as used herein, means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. Exemplary monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, and the like.

The term "cycloalkenyl" as used herein, means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. Exemplary monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. An exemplary multicyclic cycloalkenyl is norbornylenyl.

The term "aryl" as used herein, means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. Exemplary aryl groups include phenyl or naphthyl, or phenyl substituted or naphthyl substituted.

The term "fluorobenzyl" as used herein, means a benzyl group wherein the phenyl moiety is substituted with one or more fluorine atoms.

5 The term "alkenyl", as used herein, is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl.

10 The term "alkynyl" as used herein, is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

15 The term "Halo" or "halogen" as used herein, refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

20 The term "carbocycle" or "carbocyclic residue" as used herein, is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic, any of which may be saturated (i.e. a cycloalkyl moiety), partially unsaturated (i.e. a cycloalkenyl moiety), or aromatic
25 (i.e. an aryl moiety). Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane,
30 [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

The term "heterocycle" or "heterocyclic system" as used herein, is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is a saturated heterocyclic ring (i.e. a heterocyclyl moiety), a partially unsaturated heterocyclic ring (i.e. a heterocyclenyl moiety), or an unsaturated heterocyclic ring (i.e. a heteroaryl moiety), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl,

imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, 5 naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, 10 phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, 15 pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 20 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles 25 include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused 30 ring and spiro compounds containing, for example, the above heterocycles.

The term "aromatic heterocyclic system" or "heteroaryl" as used herein, means an aromatic

monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur.

Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide.

Heteroaryl as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary heteroaryl and substituted heteroaryl groups include pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindole, 1,2,4-triazinyl, benzthiazolyl, furanyl, imidazolyl, indolyl, indoliziny, isoxazolyl, isoquinoliny, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl,

pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl.

The term "heterocyclenyl" as used herein, means a
5 non-aromatic monocyclic or multicyclic hydrocarbon ring
system of about 3 to about 10 carbon atoms, preferably
about 5 to about 10 carbon atoms, in which one or more
of the carbon atoms in the ring system is/are hetero
element(s) other than carbon, for example nitrogen,
10 oxygen or sulfur atoms, and which contains at least one
carbon-carbon double bond or carbon-nitrogen double
bond. It is preferred that the total number of S and O
atoms in the heterocyclenyl is not more than 1.
Preferred ring sizes of rings of the ring system include
15 about 5 to about 6 ring atoms. The designation of the
aza, oxa or thia as a prefix before heterocyclenyl
define that at least a nitrogen, oxygen or sulfur atom
is present respectively as a ring atom. The nitrogen
atom of an heterocyclenyl may be a basic nitrogen atom.
20 The nitrogen or sulphur atom of the heterocyclenyl may
also be optionally oxidized to the corresponding
N-oxide, S-oxide or S,S-dioxide. "Heterocyclenyl" as
used herein includes by way of example and not
limitation those described in Paquette, Leo A. ;
25 "Principles of Modern Heterocyclic Chemistry" (W. A.
Benjamin, New York, 1968), particularly Chapters 1, 3,
4, 6, 7, and 9; "The Chemistry of Heterocyclic
Compounds, A series of Monographs" (John Wiley & Sons,
New York, 1950 to present), in particular Volumes 13,
30 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566
(1960). Exemplary monocyclic azaheterocyclenyl groups
include 1,2,3,4- tetrahydrohydropyridine,
1,2-dihydropyridyl, 1,4-dihydropyridyl,

1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazoliny, 2-pyrazoliny, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, 5 dihydrofuranyl, and fluorodihydrofuranyl. Preferred is dihydrofuranyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Preferred monocyclic thiaheterocyclenyl rings include dihydrothiophenyl and dihydrothiopyranyl; more preferred 10 is dihydrothiophenyl.

The term "heterocyclyl" as used herein, means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more 15 of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Preferred ring sizes of rings of the ring 20 system include about 5 to about 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The nitrogen atom of an heterocyclyl may be a basic nitrogen 25 atom. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. "Heterocyclyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of 30 Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to

present), in particular Volumes 13, 14, 16, 19, and 28;
and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary
monocyclic heterocyclyl rings include piperidyl,
pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl,
5 thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl,
tetrahydrofuranyl, tetrahydrothiophenyl,
tetrahydrothiopyranyl, and the like.

The term "amino acid" as used herein means an
organic compound containing both a basic amino group and
10 an acidic carboxyl group. Included within this term are
natural amino acids (e.g., L-amino acids), modified and
unusual amino acids (e.g., D-amino acids), as well as
amino acids which are known to occur biologically in
free or combined form but usually do not occur in
15 proteins. Included within this term are modified and
unusual amino acids, such as those disclosed in, for
example, Roberts and Vellaccio (1983) The Peptides, 5:
342-429, the teaching of which is hereby incorporated by
reference. Natural protein occurring amino acids
20 include, but are not limited to, alanine, arginine,
asparagine, aspartic acid, cysteine, glutamic acid,
glutamine, glycine, histidine, isoleucine, leucine,
lysine, methionine, phenylalanine, serine, threonine,
tyrosine, tyrosine, tryptophan, proline, and valine.
25 Natural non-protein amino acids include, but are not
limited to arginosuccinic acid, citrulline, cysteine
sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine,
homoserine, ornithine, 3-monoiodotyrosine,
3,5-diiodotyrosine, 3,5,5'-triiodothyronine, and
30 3,3',5,5'-tetraiodothyronine. Modified or unusual amino

acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, 2,4-diaminobutyric acid, homoarginine, 5 norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, β -phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic 10 acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 15 2-benzyl-5-aminopentanoic acid.

The term "peptide" as used herein means a linear compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. A "peptide" as used in the presently claimed 20 invention is intended to refer to a moiety with a molecular weight of less than 10,000 Daltons, preferable less than 5,000 Daltons, and more preferably less than 2,500 Daltons. The term "peptide" also includes compounds containing both peptide and non-peptide 25 components, such as pseudopeptide or peptidomimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

30 The term "pseudopeptide" or "peptidomimetic" as used herein, is a compound which mimics the structure of

an amino acid residue or a peptide, for example, by using linking groups other than amide linkages between the peptide mimetic and an amino acid residue (pseudopeptide bonds) and/or by using non-amino acid substituents and/or a modified amino acid residue. A "pseudopeptide residue" means that portion of an pseudopeptide or peptidomimetic that is present in a peptide.

The term "peptide bond" as used herein, means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

The term "pseudopeptide bonds" as used herein, includes peptide bond isosteres which may be used in place of or as substitutes for the normal amide linkage. These substitute or amide "equivalent" linkages are formed from combinations of atoms not normally found in peptides or proteins which mimic the spatial requirements of the amide bond and which should stabilize the molecule to enzymatic degradation.

The term "non-peptide" as used herein, refers to a compound comprised of preferably less than three amide bonds in the backbone core compound or preferably less than three amino acids or amino acid mimetics.

The phrase "pharmaceutically acceptable" as used herein, is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salts" as used herein, refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The term "pharmaceutically acceptable prodrugs" as used herein means those prodrugs of the compounds useful according to the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed *in vivo* to yield the parent

compound of the above formula, for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, K. Widder et al,

Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery
5 Reviews, H. Bundgaard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77; p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692, 1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible
10 Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to
15 survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The coordination sphere of the radionuclide includes all the ligands or groups bound to the
20 radionuclide. For a transition metal radionuclide, M_t , to be stable it typically has a coordination number (number of donor atoms) comprised of an integer greater than or equal to 4 and less than or equal to 9; that is there are 4 to 9 atoms bound to the metal and it is said
25 to have a complete coordination sphere. The requisite coordination number for a stable radionuclide complex is determined by the identity of the radionuclide, its oxidation state, and the type of donor atoms.

Lyophilization aids useful in the preparation of
30 diagnostic kits useful for the preparation of radiopharmaceuticals include but are not limited to

mannitol, lactose, sorbitol, dextran, Ficoll, and polyvinylpyrrolidone (PVP).

Stabilization aids useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to ascorbic acid, cysteine, monothioglycerol, sodium bisulfite, sodium metabisulfite, gentisic acid, and inositol.

Solubilization aids useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to ethanol, glycerin, polyethylene glycol, propylene glycol, polyoxyethylene sorbitan monooleate, sorbitan monooleate, polysorbates, poly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymers (Pluronic) and lecithin. Preferred solubilizing aids are polyethylene glycol, and Pluronic.

Bacteriostats useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to benzyl alcohol, benzalkonium chloride, chlorbutanol, and methyl, propyl or butyl paraben.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can

also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may
5 be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes
10 used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

The present invention is intended to include all isotopes of atoms occurring in the present compounds.
15 Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

20 When any variable (e.g., R^9) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2
25 R^9 , then said group may optionally be substituted with up to two R^9 groups and R^9 at each occurrence is selected independently from the definition of R^9 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable
30 compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such

substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may
5 be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The pharmaceutically acceptable salts of the
10 present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the
15 appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical*
20 *Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g.,
25 solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions
30 containing the same.

SYNTHESIS OF NEW MACROCYCLES

Hydroxypyridinones are monobasic and form stable metal complexes with hard trivalent metal ions, such as Fe^{3+} , In^{3+} and Ln^{3+} . Compared to catechols and hydroxymates, hydroxy-pyridinones have relatively low pKa values (5 - 9). Hydroxypyridinones also have high selectivity in bonding to trivalent metal ions. As a result, chelators based on hydroxypyridinones have been used for Fe detoxification. In the present invention, the hydroxypyridinone moiety is used as a part of a macrocyclic chelant using the hydroxy-oxygen and amine-nitrogen for metal bonding.

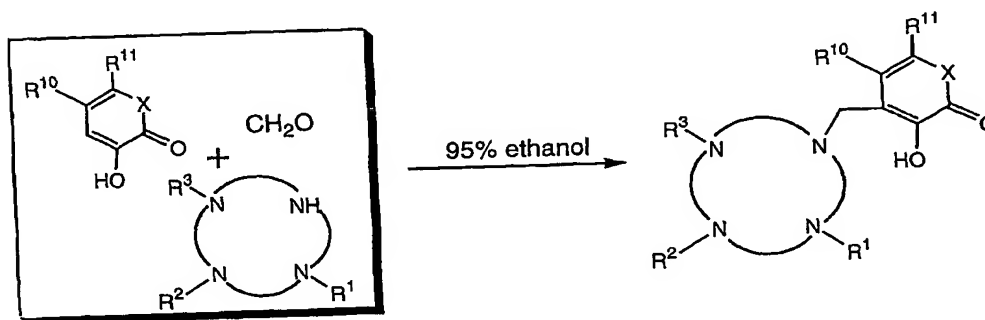
Macrocyclic Chelants Containing a Substituted 3-Hydroxy-2(1H)-Pyridinone Group

One aspect of this invention involves synthesis of macrocyclic chelants containing a substituted 3-hydroxy-2-(1H)-pyridinone group, and their potential use as BFCs for the radiolabeling of biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. Recently, Taylor and coworkers (Patel, M. K., Fox, R., and Taylor, P. D. *Tetrahedron* **1996**, *52*, 1835-1840) reported a Mannich reaction of a secondary amine with 3-hydroxy-2-(1H)-pyridinone in the presence of formaldehyde. It was found that the Mannich base obtained from 3-hydroxy-2-(1H)-pyridinone is aminomethylated at C4 (the ortho-position of the hydroxy group) and not at C6 position of the pyridinone ring. The C4 mono-substituted Mannich base is formed even at the room temperature. In the present invention, the same approach (Scheme I) was used to prepare macrocyclic chelants containing 3-hydroxy-2-(1H)-pyridinone groups. The key step is the preparation of the hydroxypyridinone intermediate. For example, 1-[(ethylox-

carbonyl)methyl]-3-hydroxy-2-(1H)-pyridinone (HPE) was prepared according to the literature procedure (Streater, M. et al, *J. Med. Chem.* **1990**, 33, 1749-1755).

5

Scheme I. Synthesis of Macrocyclic Chelants Containing Substituted 3-Hydroxy-2-(1H)-Pyridinone Moiety



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Macrocyclic chelants containing a 3-hydroxy-2-(1H)-pyridinone group are of particular interest as BFCs for the radiolabeling of biomolecules. The biomolecule can be attached to the pyridinone-nitrogen via a direct bond or a linker. It can also be attached to the functional groups (R^{10} and R^{11}). The advantage of using these macrocyclic chelants as BFCs is that the attachment of biomolecule does not create any extra chiral center on the chelants themselves. The biomolecules include antibodies, peptides, peptidomimetics, and non-peptide receptor ligands.

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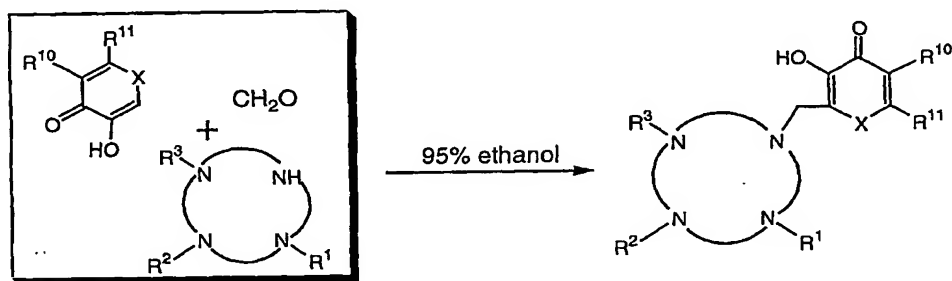
Macrocyclic Chelants Containing Substituted 3-Hydroxy-4-(1H)-Pyridinone Groups

Another aspect of this invention involves synthesis of macrocyclic chelants containing a

25

substituted 3-hydroxy-4-(1H)-pyridinone group, and their potential use as BFCs for the radiolabeling of biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. Like 3-hydroxy-2-(1H)-pyridinones, 3-hydroxy-4-(1H)-pyridinone analogs can also undergo the Mannich reaction with a secondary amine in the presence of formaldehyde. The position of aminomethylation is expected to be at C2 (the ortho-position of the hydroxy group). Scheme II shows the general scheme for the synthesis of macrocyclic chelants containing a substituted 3-hydroxy-4-(1H)-pyridinone moiety. Preparation of the substituted 3-hydroxy-4-(1H)-pyridinone intermediates can be accomplished by following procedures described in prior literature (Molenda, J. J. et al. *J. Med. Chem.* **1994**, 37, 93-98).

Scheme II. Synthesis of Macrocyclic Chelants Containing Substituted 3-Hydroxy-4-(1H)-Pyridinone Moiety



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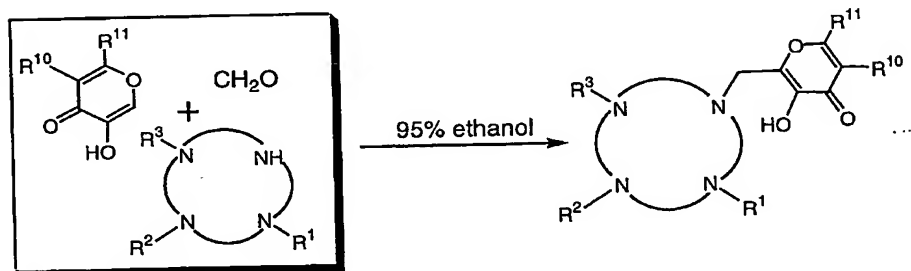
Macrocyclic Chelants Containing Substituted 3-Hydroxy-Pyran-4-one Groups

Another aspect of this invention involves synthesis of macrocyclic chelants containing a substituted 3-hydroxy-pyran-4-one group, and their potential use as BFCs for the radiolabeling of

25

biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. Taylor and coworkers (Fox, R. C. and Taylor, P. D. *Synth. Commun.* **1998**, *28*, 3983-3989) also reported a Mannich reaction of a piperazine with
 5 kojic acid (5-hydroxy-2-hydroxymethyl-pyran-4-one) in the presence of formaldehyde. The reaction was performed at room temperature. Using the same approach, macrocyclic chelants containing a 3-hydroxy-pyran-4-one group can be synthesized by reacting 3-hydroxy-pyran-4-one
 10 one with the tri-substituted macrocyclic tetraamine in the presence of formaldehyde according to Scheme III.

Scheme III. Synthesis of Macrocyclic Chelants
 Containing
 15 Substituted 3-Hydroxy-Pyran-4-one Moiety



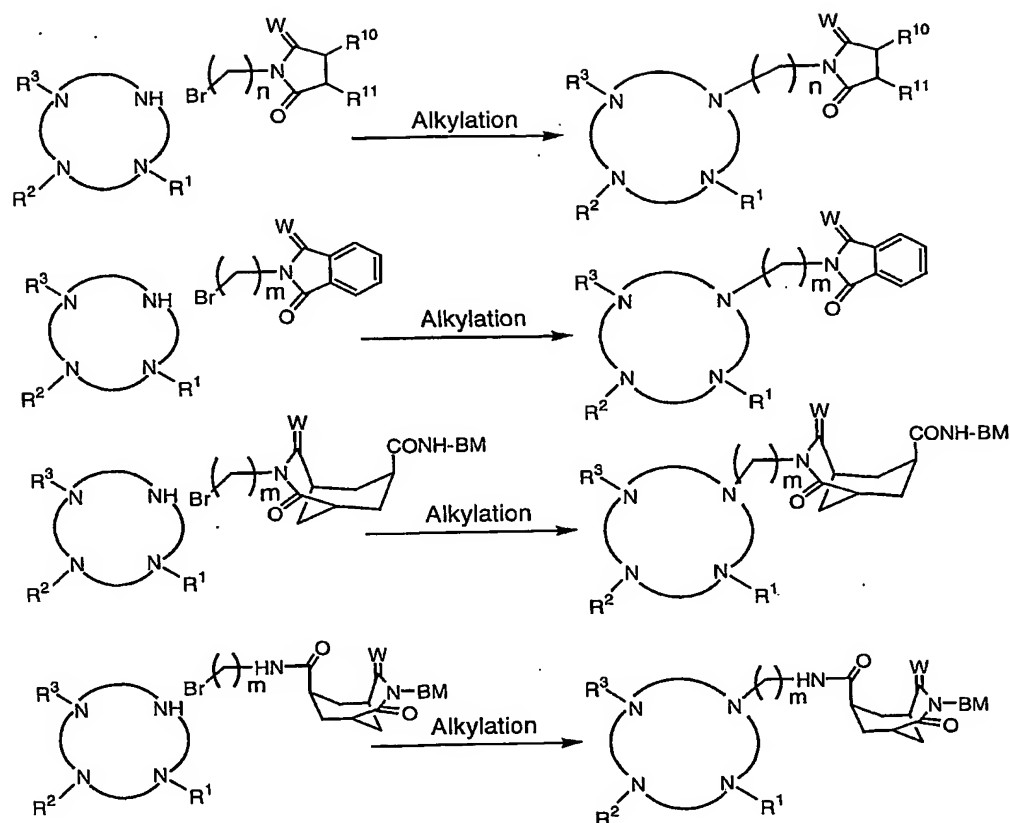
20 **Macrocyclic Chelants Containing Substituted Succinimide or Phthalimide Groups.**

Another aspect of this invention involves synthesis of macrocyclic chelants containing a substituted succinimide or phthalimide group, and their potential use as BFCs for the radiolabeling of biomolecules or
 25 their lanthanide complexes as NMR or X-ray contrast agents. In these macrocyclic chelants, the succinimide

or phthalimide moiety is connected to one of the four amine-nitrogen atoms of the macrocycle via a C₁-C₃ alkylene linker in such a way that the carbonyl-O atom of the succinamide or phthalimide group is expected to coordinate the lanthanide metal ions to form 8- or 9-coordinated metal chelates. Due to the presence of D03A chelating unit, these macrocyclic chelants will form lanthanide metal chelates with high thermodynamic stability and kinetic inertness. Scheme IV shows a general procedure for the synthesis of macrocyclic chelants containing a succinimide or phthalimide group. The tri-substituted tetraamine reacts with a N-(bromoalkyl)succinimide or N-(bromoalkyl)phthalimide in the presence of a base such as potassium carbonate or triethylamine to give the expected product. If these macrocyclic chelants are used as BFCs for the radiolabeling of biomolecules, the biomolecule can be attached to the 5-membered succinimide ring via a direct bond or a linker. It can also be attached to the functional groups (R¹⁰ and R¹¹). The attachment of biomolecule does not create any extra chiral center on the chelants. The biomolecules include antibodies, antibody fragments, peptides, peptidomimetics, and non-peptide receptor ligands.

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Scheme IV. Synthesis of Macrocyclic Chelants Containing a Succinimide or Phthalimide group.



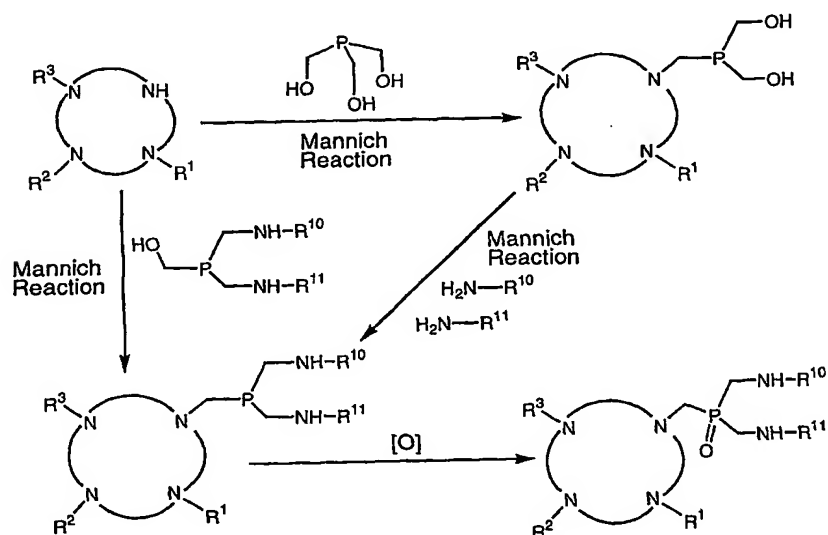
Macrocyclic Chelants Derivatized from Tris(hydroxymethyl)phosphine

5 Another aspect of this invention involves synthesis of macrocyclic chelants derivatized from tris(hydroxymethyl)phosphine (THP) and their potential use as BFCs for the radiolabeling of biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. It is known that hydroxymethylphosphines undergo the Mannich reactions with primary and secondary amines (Märkl, V. G., et al. *Tetrahedron Letters*, 1980, 21, 1409-1412). Mannich reactions have been extensively reviewed (Tramotini, M. and Angiolini, L. *Tetrahedron*,

10

1990, 1791-1823; Tramotini, M. *SYNTHESIS*, 1976, 703-775). Recently, Mannich reactions of hydroxymethylphosphines with amines, amino acids, and peptides (Katti, K. V. et al, *J. Am. Chem. Soc.* 1999, 121, 1658-1664) were reported. In the present invention, the Mannich reaction (Scheme V) of hydroxymethylphosphine with one equivalent of a secondary diamine at pH 3 - 5 is used to produce new macrocyclic chelants. Oxidation of the phosphine(III) atom of the macrocyclic chelant results in macrocyclic chelants phosphine-oxo group.

Scheme V. Synthesis of Macrocyclic Chelants Derivatized from Tris(hydroxymethyl)phosphine.

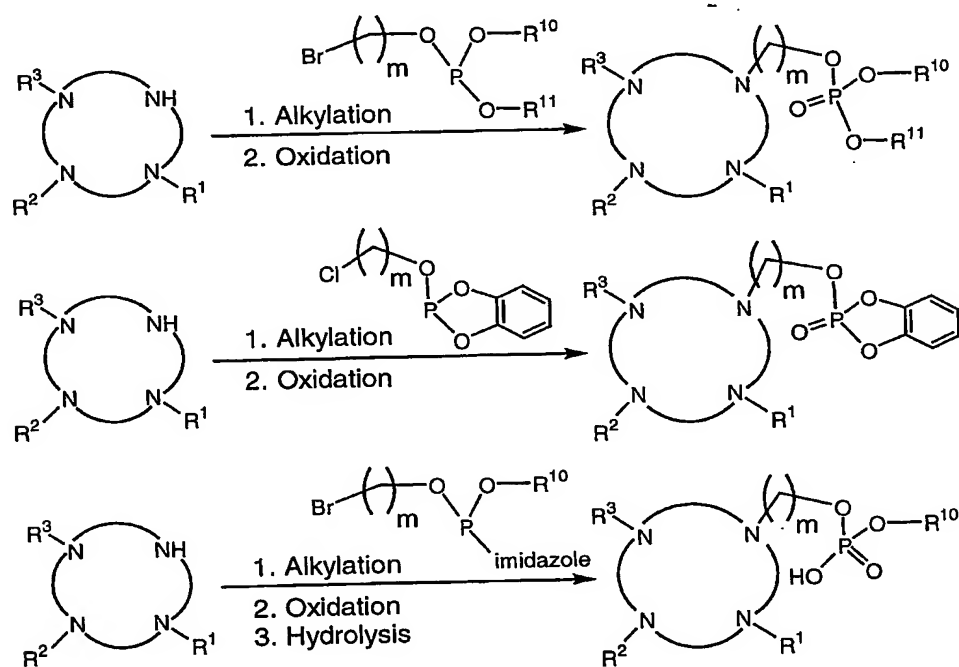


Macrocyclic chelants containing a phosphine-oxo group are of interest because phosphine-oxo oxygen can coordinate the lanthanide metal ions to form 8- or 9-

coordinated metal chelates. These macrocyclic chelants are expected to form metal chelates with high thermodynamic stability and kinetic inertness. They can also be used as BFCs for the radiolabeling of

5 biomolecules. The biomolecule can be attached to the functional groups (R^{10} and R^{11}). The biomolecules include antibodies, antibody fragments, peptides, peptidomimetics, and non-peptide receptor ligands.

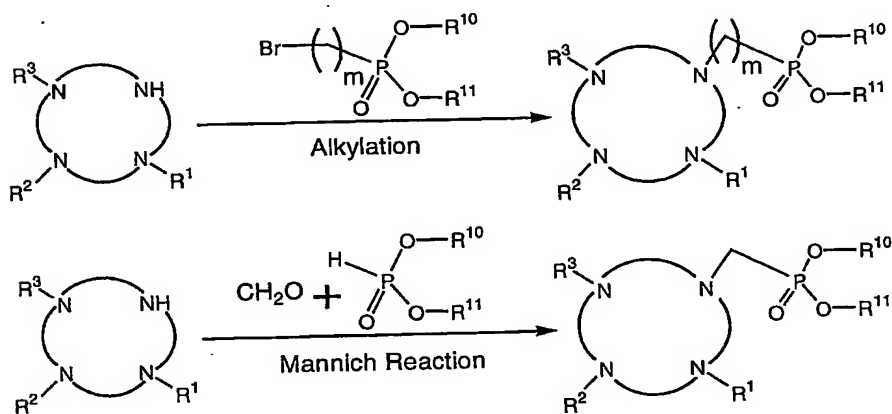
10 Scheme VI. Synthesis of Macrocyclic Chelants Derivatized from Phosphoric Triesters.



Macrocyclic Chelants Derivatized from Phosphoric Triester

Another aspect of this invention involves synthesis of macrocyclic chelants derivatized from phosphoric triesters, and their potential use as BFCs for the radiolabeling of biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. Synthesis of macrocyclic chelants can be achieved by reacting the tri-substituted macrocyclic tetraamine with bromoalkylphosphite in the presence of a base, such as triethylamine, followed by oxidation of the phosphite to give the corresponding phosphoric triester. The chloro- or bromoalkylphosphite can be obtained from commercial sources or prepared according to procedures described in prior arts (US Patent 5,919,967).

Scheme VII. Synthesis of Macroyclic Chelants Derivatized from Phosphonic Acid Diesters.



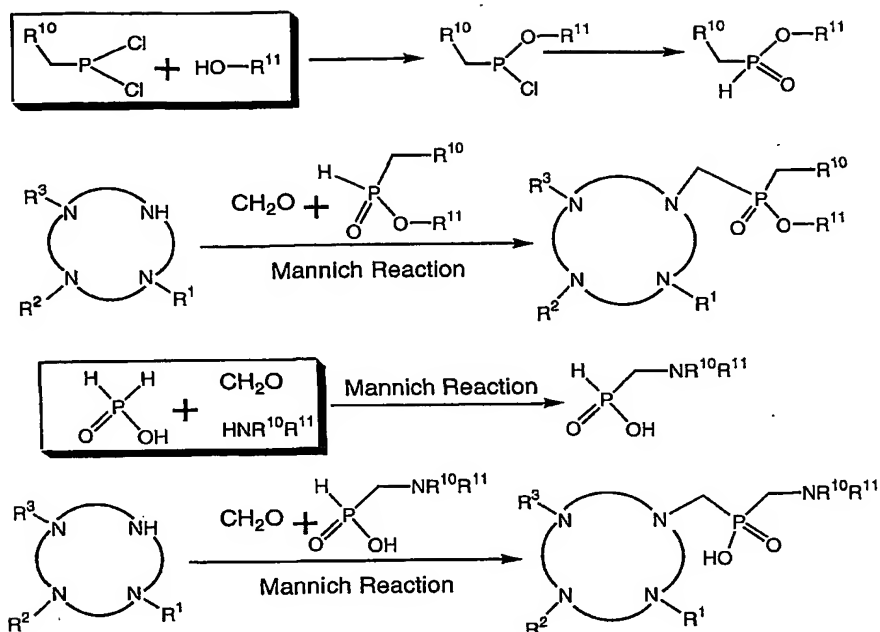
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**Macrocyclic Chelants Derivatized from Phosphonic
Acid Diester**

Another aspect of this invention involves synthesis of macrocyclic chelants derivatized from
5 phosphonic acid diesters, and their potential use as
BFCs for the radiolabeling of biomolecules or their
lanthanide complexes as NMR or X-ray contrast agents.
Synthesis (Scheme VII) of macrocyclic chelants can be
achieved by the reaction of the tri-substituted
10 macrocyclic tetraamine with bromoalkylphosphonic acid
diester in the presence of a base, such as
triethylamine. Some macrocyclic chelants can be
prepared by a Mannich reaction (Scheme VII) of the tri-
substituted macrocyclic tetraamine with phosphonic acid
15 diester in the presence of formaldehyde. The
bromoalkylphosphonic acid diester or phosphonic acid
diester can be obtained from commercial sources or
prepared according to procedures described in prior arts
(examples include Lamande, L, et al *Phosphorus Sulfur*
20 *and Silicon* **1999**, 144, 529-532; Grevy, J.-M., et al
SYNLETT. **1997**, 555-556).

Scheme VIII. Synthesis of Macrocyclic Chelants
Derivatized from Phosphinic Esters.

25



Macrocyclic Chelants Derivatized from Phosphinic Esters

5 Another aspect of this invention involves synthesis of macrocyclic chelants derivatized from phosphinic esters, and their potential use as BFCs for the radiolabeling of biomolecules or their lanthanide complexes as NMR or X-ray contrast agents. Synthesis

10 (Scheme VIII) of macrocyclic chelants can be achieved by a Mannich reaction of the tri-substituted macrocyclic tetraamine with phosphinic acid ester in the presence of formaldehyde. Some macrocyclic chelant can be prepared by reacting the tri-substituted macrocyclic tetraamine

15 with one equivalent of a semi-Mannich base in the presence of formaldehyde. Phosphinic acid and its esters can be obtained either from commercial sources or prepared according to published procedures.

Macrocyclic chelants containing a phosphinic acid or phosphinic ester are of interest because phosphinyl-oxygen or phosphinate-oxygen can coordinate the lanthanide metal ions to form 8- or 9-coordinated metal chelates with high thermodynamic stability and kinetic inertness. They can also be used as BFCs for the radiolabeling of biomolecules. The biomolecule can be attached to the functional groups (R^{10} and R^{11}). The biomolecules include antibodies, antibody fragments, peptides, peptidomimetics, and non-peptide receptor ligands.

The bio-targeted pharmaceuticals of the present invention have the formulae, $(BM)_d-L_n-(C_h-X)$, and $(BM)_d-L_n-(C_h-X^1)_{d'}$, wherein BM represents a peptide, polypeptide, peptidomimetic, or non-peptide that binds to a receptor or enzyme expressed or up-regulated in an organ or disease state, d is 1-10, L_n represents an optional linking group, C_h represents a novel metal chelator of the present invention, d' is 1-100, X represents a radioisotope, and X^1 represents a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83 or 90.

The pharmaceuticals of the present invention can be synthesized by several approaches. One approach involves the synthesis of the targeting peptide, polypeptide, peptidomimetic or non-peptide moiety, BM, and direct attachment of one or more moieties, BM, to one or more metal chelators, C_h . Another approach involves the attachment of one or more moieties, BM, to the linking group, L_n , which is then attached to one or more metal chelators, C_h . Another approach, useful in the synthesis of pharmaceuticals wherein d is 1, involves the synthesis of the moiety, $BM-L_n$, together,

by incorporating a group bearing L_n into the synthesis of the peptide, polypeptide, peptidomimetic, or non-peptide. The resulting moiety, $BM-L_n$, is then attached to one or more metal chelators, C_h . Another approach
5 involves the synthesis of a peptide, polypeptide, peptidomimetic, or non-peptide, BM , bearing a fragment of the linking group, L_n , one or more of which are then attached to the remainder of the linking group and then to one or more metal chelators, C_h .

10 The peptides, polypeptides, peptidomimetics and non-peptides, BM , optionally bearing a linking group, L_n , or a fragment of the linking group, can be synthesized using standard synthetic methods known to those skilled in the art. Preferred methods include but
15 are not limited to those methods described below.

Generally, peptides, polypeptides, and peptidomimetics are elongated by deprotecting the alpha-amine of the C-terminal residue and coupling the next suitably protected amino acid through a peptide
20 linkage using the methods described. This deprotection and coupling procedure is repeated until the desired sequence is obtained. This coupling can be performed with the constituent amino acids in a stepwise fashion, or condensation of fragments (two to several amino
25 acids), or combination of both processes, or by solid phase peptide synthesis according to the method originally described by Merrifield (*J. Am. Chem. Soc.* **1963** 85, 2149-2154), the disclosure of which is hereby incorporated by reference.

30 The peptides, polypeptides and peptidomimetics may also be synthesized using automated synthesizing

equipment. In addition to the foregoing, procedures for peptide, polypeptide and peptidomimetic synthesis are described in Stewart and Young, "Solid Phase Peptide Synthesis", 2nd ed, Pierce Chemical Co., Rockford, IL
5 (1984); Gross, Meienhofer, Udenfriend, Eds., "The Peptides: Analysis, Synthesis, Biology, Vol. 1, 2, 3, 5, and 9, Academic Press, New York, (1980-1987); Bodanszky, "Peptide Chemistry: A Practical Textbook", Springer-Verlag, New York (1988); and Bodanszky et al.
10 "The Practice of Peptide Synthesis" Springer-Verlag, New York (1984), the disclosures of which are hereby incorporated by reference.

The coupling between two amino acid derivatives, an amino acid and a peptide, polypeptide or peptidomimetic,
15 two peptide, polypeptide or peptidomimetic fragments, or the cyclization of a peptide, polypeptide or peptidomimetic can be carried out using standard coupling procedures such as the azide method, mixed carbonic acid anhydride (isobutyl chloroformate) method,
20 carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimides) method, active ester (p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, Woodward reagent K method, carbonyldiimidazole method, phosphorus
25 reagents such as BOP-Cl, or oxidation-reduction method. Some of these methods (especially the carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole. These coupling reactions may be performed in either solution (liquid phase) or solid phase.

30 The functional groups of the constituent amino acids or amino acid mimetics must be protected during the coupling reactions to avoid undesired bonds being

formed. The protecting groups that can be used are listed in Greene, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference.

The alpha-carboxyl group of the C-terminal residue is usually protected by an ester that can be cleaved to give the carboxylic acid. These protecting groups include: 1) alkyl esters such as methyl and t-butyl, 2) aryl esters such as benzyl and substituted benzyl, or 3) esters which can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters. In the solid phase case, the C-terminal amino acid is attached to an insoluble carrier (usually polystyrene). These insoluble carriers contain a group which will react with the carboxyl group to form a bond which is stable to the elongation conditions but readily cleaved later. Examples of which are: oxime resin (DeGrado and Kaiser (1980) *J. Org. Chem.* **45**, 1295-1300) chloro or bromomethyl resin, hydroxymethyl resin, and aminomethyl resin. Many of these resins are commercially available with the desired C-terminal amino acid already incorporated.

The alpha-amino group of each amino acid must be protected. Any protecting group known in the art can be used. Examples of these are: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc);

3) aliphatic carbamate types such as
tert-butyloxycarbonyl (Boc), ethoxycarbonyl,
diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4)
cyclic alkyl carbamate types such as
5 cyclopentylloxycarbonyl and adamantylloxycarbonyl; 5)
alkyl types such as triphenylmethyl and benzyl; 6)
trialkylsilane such as trimethylsilane; and 7) thiol
containing types such as phenylthiocarbonyl and
dithiasuccinoyl. The preferred alpha-amino protecting
10 group is either Boc or Fmoc. Many amino acid or amino
acid mimetic derivatives suitably protected for peptide
synthesis are commercially available.

The alpha-amino protecting group is cleaved prior
to the coupling of the next amino acid. When the Boc
15 group is used, the methods of choice are trifluoroacetic
acid, neat or in dichloromethane, or HCl in dioxane.
The resulting ammonium salt is then neutralized either
prior to the coupling or in situ with basic solutions
such as aqueous buffers, or tertiary amines in
20 dichloromethane or dimethylformamide. When the Fmoc
group is used, the reagents of choice are piperidine or
substituted piperidines in dimethylformamide, but any
secondary amine or aqueous basic solutions can be used.
The deprotection is carried out at a temperature between
25 0 °C and room temperature.

Any of the amino acids or amino acid mimetics
bearing side chain functionalities must be protected
during the preparation of the peptide using any of the
above-identified groups. Those skilled in the art will
30 appreciate that the selection and use of appropriate
protecting groups for these side chain functionalities
will depend upon the amino acid or amino acid mimetic

and presence of other protecting groups in the peptide, polypeptide or peptidomimetic. The selection of such a protecting group is important in that it must not be removed during the deprotection and coupling of the
5 alpha-amino group.

For example, when Boc is chosen for the alpha-amine protection the following protecting groups are acceptable: *p*-toluenesulfonyl (tosyl) moieties and nitro for arginine; benzyloxycarbonyl, substituted
10 benzyloxycarbonyls, tosyl or trifluoroacetyl for lysine; benzyl or alkyl esters such as cyclopentyl for glutamic and aspartic acids; benzyl ethers for serine and threonine; benzyl ethers, substituted benzyl ethers or 2-bromobenzyloxycarbonyl for tyrosine; *p*-methylbenzyl,
15 *p*-methoxybenzyl, acetamidomethyl, benzyl, or *t*-butylsulfonyl for cysteine; and the indole of tryptophan can either be left unprotected or protected with a formyl group.

When Fmoc is chosen for the alpha-amine protection
20 usually *tert*-butyl based protecting groups are acceptable. For instance, Boc can be used for lysine, *tert*-butyl ether for serine, threonine and tyrosine, and *tert*-butyl ester for glutamic and aspartic acids.

Once the elongation of the peptide, polypeptide or
25 peptidomimetic, or the elongation and cyclization of a cyclic peptide or peptidomimetic is completed all of the protecting groups are removed. For the liquid phase synthesis the protecting groups are removed in whatever manner as dictated by the choice of protecting groups.
30 These procedures are well known to those skilled in the art.

When a solid phase synthesis is used to synthesize a cyclic peptide or peptidomimetic, the peptide or peptidomimetic should be removed from the resin without simultaneously removing protecting groups from functional groups that might interfere with the cyclization process. Thus, if the peptide or peptidomimetic is to be cyclized in solution, the cleavage conditions need to be chosen such that a free α -carboxylate and a free α -amino group are generated without simultaneously removing other protecting groups. Alternatively, the peptide or peptidomimetic may be removed from the resin by hydrazinolysis, and then coupled by the azide method. Another very convenient method involves the synthesis of peptides or peptidomimetics on an oxime resin, followed by intramolecular nucleophilic displacement from the resin, which generates a cyclic peptide or peptidomimetic (Osapay, Profit, and Taylor (1990) *Tetrahedron Letters* 43, 6121-6124). When the oxime resin is employed, the Boc protection scheme is generally chosen. Then, the preferred method for removing side chain protecting groups generally involves treatment with anhydrous HF containing additives such as dimethyl sulfide, anisole, thioanisole, or p-cresol at 0 °C. The cleavage of the peptide or peptidomimetic can also be accomplished by other acid reagents such as trifluoromethanesulfonic acid/trifluoroacetic acid mixtures.

Unusual amino acids used in this invention can be synthesized by standard methods familiar to those skilled in the art ("The Peptides: Analysis, Synthesis, Biology, Vol. 5, pp. 342-449, Academic Press, New York (1981)). N-Alkyl amino acids can be prepared using

procedures described in previously (Cheung et al., (1977) *Can. J. Chem.* **55**, 906; Freidinger et al., (1982) *J. Org. Chem.* **48**, 77 (1982)), which are incorporated herein by reference.

5 Additional synthetic procedures that can be used by one of skill in the art to synthesize the peptides, polypeptides and peptidomimetics targeting moieties are described in U.S. Patent No. 5,879,657, the contents of which are herein incorporated by reference.

10 The attachment of linking groups, L_n , to the peptides, polypeptides, peptidomimetics and non-peptide, BM; chelators, C_h , to the peptides, polypeptides, peptidomimetics, and non-peptides, BM, or to the linking groups, L_n ; and peptides, polypeptides, peptidomimetics,
15 and non-peptides bearing a fragment of the linking group to the remainder of the linking group, in combination forming the moiety, $(BM)_d-L_n$, and then to the moiety C_h ; can all be performed by standard techniques. These
include, but are not limited to, amidation,
20 esterification, alkylation, and the formation of ureas or thioureas. Procedures for performing these attachments can be found in Brinkley, M., *Bioconjugate Chemistry* **1992**, 3(1), which is incorporated herein by reference.

25 The linking group L_n can serve several roles. First it provides a spacing group between the metal chelator, and the one or more of the peptides, polypeptides, peptidomimetics, or non-peptides, BM, so as to minimize the possibility that the moieties C_h-X ,
30 C_h-X^1 , will interfere with the interaction of the recognition sequences of BM with the target receptors.

The necessity of incorporating a linking group in a reagent is dependent on the identity of BM, C_h-X , and C_h-X^1 . If C_h-X , and C_h-X^1 , cannot be attached to BM without substantially diminishing its affinity for the
5 receptors, then a linking group is used. A linking group also provides a means of independently attaching multiple peptides, polypeptides, peptidomimetics, and non-peptides, BM, to one group that is attached to C_h-X , or C_h-X^1 .

10 The linking group also provides a means of incorporating a pharmacokinetic modifier into the pharmaceuticals of the present invention. The pharmacokinetic modifier serves to direct the biodistribution of the injected pharmaceutical other than
15 by the interaction of the targeting moieties, BM, with the target receptors. A wide variety of functional groups can serve as pharmacokinetic modifiers, including, but not limited to, carbohydrates, polyalkylene glycols, peptides or other polyamino acids,
20 and cyclodextrins. The modifiers can be used to enhance or decrease hydrophilicity and to enhance or decrease the rate of blood clearance. The modifiers can also be used to direct the route of elimination of the pharmaceuticals. Preferred pharmacokinetic modifiers
25 are those that result in moderate to fast blood clearance and enhanced renal excretion.

For the diagnosis of thromboembolic disorders or atherosclerosis, BM is selected from the group including the cyclic IIb/IIIa receptor antagonist compounds
30 described in U.S. Patent No. 5,879,657; the RGD

containing peptides described in U.S. Patent Nos.
4,578,079, 4,792,525, the applications PCT US88/04403,
PCT US89/01742, PCT US90/03788, PCT US91/02356 and by
Ojima et. al., 204th Meeting of the Amer. Chem. Soc.,
5 1992, Abstract 44; the peptides that are fibrinogen
receptor antagonists described in European Patent
Applications 90/202015.5, 90/202030.4, 90/202032.2,
90/202032.0, 90/311148.2, 90/311151.6, 90/311537.6, the
specific binding peptides and polypeptides described as
10 IIb/IIIa receptor ligands, ligands for the
polymerization site of fibrin, laminin derivatives,
ligands for fibrinogen, or thrombin ligands in PCT WO
93/23085 (excluding the technetium binding groups); the
oligopeptides that correspond to the IIIa protein
15 described in PCT WO90/00178; the hirudin-based peptides
described in PCT WO90/03391; the IIb/IIIa receptor
ligands described in PCT WO90/15818; the thrombus,
platelet binding or atherosclerotic plaque binding
peptides described in PCT WO92/13572 (excluding the
20 technetium binding group) or GB 9313965.7; the fibrin
binding peptides described in U.S. Patent Nos. 427,646
and 5,270,030; the hirudin-based peptides described in
U.S. Patent No. 5,279,812; or the fibrin binding
proteins described in U.S. Patent 5,217,705; the guanine
25 derivatives that bind to the IIb/IIIa receptor described
in U.S. Patent No. 5,086,069; or the tyrosine
derivatives described in European Patent Application
0478328A1, and by Hartman et. al., J. Med. Chem., 1992,
35, 4640; or oxidized low density lipoprotein (LDL).

For the diagnosis of infection, inflammation or transplant rejection, BM is selected from the group including the leukocyte binding peptides described in PCT WO93/17719 (excluding the technetium binding group),
5 PCT WO92/13572 (excluding the technetium binding group) or U.S. Ser. No. 08-140000; the chemotactic peptides described in Eur. Pat. Appl. 90/108734.6 or A. Fischman et. al., Semin. Nuc. Med., 1994, 24, 154; the
10 leukostimulatory agents described in U.S. Patent No. 5,277,892; or the LTB4 antagonists described in PCT publication no. WO98/15295.

For the diagnosis of cancer, BM is selected from the group of somatostatin analogs described in UK Application 8927255.3 or PCT WO94/00489, the selectin
15 binding peptides described in PCT WO94/05269, the biological-function domains described in PCT WO93/12819, Platelet Factor 4 or the growth factors (PDGF, VEGF, EGF, FGF, TNF MCSF or the interleukins Il1-8).

BM may also be a compound that binds a receptor
20 that is expressed or upregulated in angiogenic tumor vasculature. For targeting the VEGF receptors, Flk-1/KDR, Flt-1, and neuropilin-1, the targeting moieties are comprised of peptides, polypeptides or
25 peptidomimetics that bind with high affinity to the receptors. For example, peptides comprised of a 23 amino acid portion of the C-terminal domain of VEGF have been synthesized which competitively inhibit binding of VEGF to VEGFR (Soker, et. al., J. Biol. Chem., 1997, 272, 31582-8). Linear peptides of 11 to 23 amino acid
30 residues that bind to the basic FGF receptor (bFGFR) are described by Cosic et. al., Mol. and Cell. Biochem., 1994, 130, 1-9. A preferred linear peptide antagonist

of the bFGFR is the 16 amino acid peptide, Met-Trp-Tyr-Arg-Pro-Asp-Leu-Asp-Glu-Arg-Lys-Gln-Gln-Lys-Arg-Glu. Gho et. al. (Cancer Research, 1997, 57, 3733-40) describe the identification of small peptides that bind
5 with high affinity to the angiogenin receptor on the surface of endothelial cells. A preferred peptide is Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg, in which the two Cys residues form an intramolecular disulfide bond. Yayon et. al. (Proc.
10 Natl. Acad. Sci, USA, 1993, 90, 10643-7) describe other linear peptide antagonists of FGFR, identified from a random phage-displayed peptide library. Two linear octapeptides, Ala-Pro-Ser-Gly-His-Tyr-Lys-Gly and Lys-Arg-Thr-Gly-Gln-Tyr-Lys- Leu are preferred for
15 inhibiting binding of bFGF to it receptor.

Targeting moieties for integrins expressed in tumor vasculature include peptides, polypeptides and peptidomimetics that bind to $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha 5 \beta 1$, $\alpha 4 \beta 1$, $\alpha 1 \beta 1$, and $\alpha 2 \beta 2$. Pierschbacher and Rouslahti (J. Biol.
20 Chem., 1987, 262, 17294-8) describe peptides that bind selectively to $\alpha 5 \beta 1$ and $\alpha v \beta 3$. U.S. Patent No. 5,536,814 describe peptides that bind with high affinity to the integrin $\alpha 5 \beta 1$. Burgess and Lim (J. Med. Chem., 1996, 39, 4520-6) disclose the synthesis three peptides that bind
25 with high affinity to $\alpha v \beta 3$: cyclo[Arg-Gly-Asp-Arg-Gly-Asp], cyclo[Arg-Gly-Asp-Arg-Gly-D-Asp] and the linear peptide Arg-Gly-Asp-Arg-Gly-Asp. U.S. Patent Nos. 5,770,565 and 5,766,591 disclose peptides that bind with high affinity to $\alpha v \beta 3$. U.S. Patent Nos. 5,767,071 and
30 5,780,426, disclose cyclic peptides that have an exocyclic Arg amino acid that have high affinity for $\alpha v \beta 3$. Srivatsa et. al., (Cardiovascular Res., 1997, 36,

408-28) describe the cyclic peptide antagonist for $\alpha v\beta 3$,
cyclo[Ala-Arg-Gly-Asp-Mamb]. Tran et. al., (Bioorg.
Med. Chem. Lett., 1997, 7, 997-1002) disclose the cyclic
peptide cyclo[Arg-Gly-Asp-Val-Gly-Ser-BTD-Ser-Gly-Val-
5 Ala] that binds with high affinity to $\alpha v\beta 3$. Arap et.
al. (Science, 1998, 279, 377-80) describe cyclic
peptides that bind to $\alpha v\beta 3$ and $\alpha v\beta 5$, Cys-Asp-Cys-Arg-
Gly-Asp-Cys-Phe-Cys, and cyclo[Cys-Asn-Gly-Asp-Cys].
Corbett et. al. (Bioorg. Med. Chem. Lett., 1997, 7, 1371-
10 6) describe a series of $\alpha v\beta 3$ selective peptidomimetics.
And Haubner et. al., (Angew. Chem. Int. Ed. Engl., 1997,
36, 1374-89) disclose peptides and peptidomimetic $\alpha v\beta 3$
antagonists obtained from peptide libraries.

Alternative targeting moieties for tumor
15 vasculature include compounds that interact with
receptor tyrosine kinases. Receptor tyrosine kinases
(TKs) are membrane proteins, which play a key role in
the transduction of mitogenic signals across the cell to
the nucleus (Rewcastle, G. W. et al *J. Med. Chem.* **1995**,
20 38, 3482-3487; Thompson, A. M. et al *J. Med. Chem.*
1997, 40, 3915-3925). Of the many TKs that have been
identified and characterized, those of the epidermal
growth factor receptor (EGFR) family are particularly
important, and have been implicated in a variety of
25 ectopic cell proliferative processes. The over-
expression of human EGF receptor is greatly amplified in
several human tumors (Fry, D. W. *Exp. Opin. Invest.*
Drugs **1994**, 3, 577-595; Jardines, L. et al *Pathobiology*
1993, 61, 268-282), accompanied by an
30 overphosphorylation of their protein targets. This
increased phosphorylation of substrate tyrosine residues
by oncogenic TK proteins is an essential step in the

neoplastic transformation. Consequently, there has been great interest in developing inhibitors of TKs (TKIs) as anticancer drugs (Burke, T. R. Jr. *Drugs Future* 1992 17, 119-131; Chang, C. J. and Geahlen, R. *J. Nat. Prod.* 5 1992, 55, 1529-1560). The over-expression of EGF receptors in tumor cells also provides the foundation for the development of diagnostic and therapeutic radiopharmaceuticals by attaching a chelator and a radionuclide onto the TK receptor ligand (tyrosine 10 kinase inhibitor).

BM may also represent proteins, antibodies, antibody fragments, peptides, polypeptides, or peptidomimetics that bind to receptors or binding sites on other tissues, organs, enzymes or fluids. Examples 15 include the β -amyloid proteins that have been demonstrated to accumulate in patients with Alzheimer's disease, atrial natriuretic factor derived peptides that bind to myocardial and renal receptors, antimyosin antibodies that bind to areas of infarcted tissues, or 20 nitroimidazole derivatives that localize in hypoxic areas in vivo.

A conjugate of the invention may be used for the detoxification of heavy metals by using a corresponding salt form of the conjugate with a pharmaceutically 25 acceptable counterion, e.g. sodium, calcium, ammonium, or zinc.

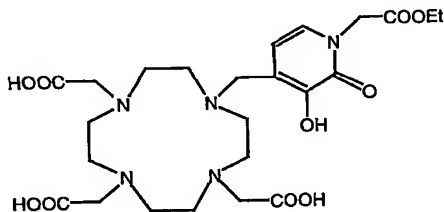
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration 30 of the invention and are not intended to be limiting thereof.

EXAMPLES

3-Hydroxy-2(1H)-pyridinone, paraformaldehyde were purchased from Aldrich. 1-[(Ethyloxcarbonyl)methyl]-3-hydroxy-2(1H)-pyridinone (HPE) was prepared according to the literature procedure (*J. Med. Chem.* **1990**, *33*, 1749-1755).

Instruments. ^1H NMR spectra were recorded on a 600 MHz Bruker spectrometer. The ^1H NMR data were reported as δ (ppm) relative to TMS. Electrospray MS analyses were performed using a VG Quattro mass spectrometer. LC-MS spectra were collected using a HP1100 LC/MSD system with API-electrospray interface. The high-performance liquid HPLC methods used a Hewlett Packard Model 1090 instrument with radiometric detector using sodium iodide probe.

Example I. Synthesis of 1,4,7,10-tetraazacyclododecane-1-{1-[(Ethyloxcarbonyl)methyl]-3-hydroxy-2(1H)-pyridinone-4-methyl}-4,7,10-triacetic acid (DO3A-HPE).



To a solution of tributyl ester of DO3A (160 mg, 0.312 mmol) in 95% ethanol (45 mL) was added HPE (68 mg, 0.342 mmol) and paraformaldehyde (20 mg, 0.67 mmol). The resulting mixture was stirred at room temperature

for 48 hours. Solvents were removed under reduced pressure to give a brownish gummy liquid, which was re-dissolved in dichloromethane (15 mL) and anhydrous TFA (10 mL). The mixture was stirred at room temperature overnight. Solvents were removed under reduced pressure. The residue was dissolved in methanol (1.5 - 2.0 mL). Upon addition of acetone (10 mL) and diethyl ether (50 mL), an off-white solid was formed. The solid was separated by filtration, washed with diethyl ether, and dried in air. The crude product was purified by HPLC with the following method:

Solvent A: 0.1% TFA
Solvent B: acetonitrile
Column: Zorbax C18 reversed phase semi-prep
column
Flow rate: 3 mL/min
Temperature: ambient
Gradient: Solvent B from 5% to 20% over 20 min.

The fractions at retention times of 10 - 12.5 min were collected. The collected fractions were combined. Solvents were removed on a rotary evaporator. The residue was dissolved in 1 mL of water, and was re-purified using a slightly different gradient:

Solvent B was isocratic (5% B) for the first 5 minutes, and then went from 5% to 20% over the next 15 min. The fractions at 13-17 min were collected. The collected fractions were combined, and lyophilized to give a white powder. The yield was 15 mg. Electrospray

MS: $M/z = 556.3$ for $[C_{24}H_{37}N_5O_{10}]^+$, 278.6 for $[C_{24}H_{38}N_5O_{10}]^{2+}$. 1H NMR (600 MHz, in D_2O , chemical

shift in ppm relative to TMS): 1.52 (t, 4H, CH₃); 3.51-
3.59 (m, 16H, CH₂, cyclen); 3.86 (m, 4H, CH₂, acetate);
4.05 (s, 2H, CH₂, acetate); 4.50 (m, 4H, CH₂/ethyl and
CH₂/methylenepyridinone); 5.06 (s, 2H, NCH₂, acetate);
5 6.82 (d, 1H, pyridinone); and 7.41 (d, 1H, pyridinone).

Example II. Synthesis of ¹⁷⁷Lu complex of DO3A-HPE.

To a shielded 5 mL vial was added 0.5 mL of DO3A-
HPE solution (100 µg/mL in 0.5 M ammonium acetate
10 buffer, pH = 7.0), followed by 50 µL of sodium gentisate
solution (10 mg/mL in 0.5 M ammonium acetate buffer, pH
= 7.0), and 10 µL of ¹⁷⁷LuCl₃ solution (100 mCi/mL in
0.05 N HCl). The total volume was 560 µL and the pH of
the reaction mixture was ~6.5. The mixture was heated
15 at 100 °C for 30 min, and then was analyzed by HPLC with
the following method:

Solvent A: 25 mM phosphate buffer, pH = 6.0

Solvent B: Acetonitrile

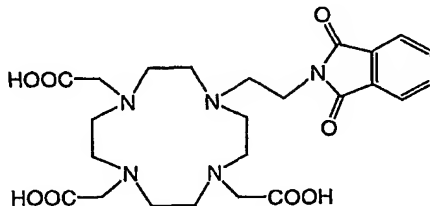
20 Column: Zorbax C18 reversed phase analytical
column

Flow rate: 1 mL/min

Gradient: Solvent B from 5% to 10% over 20
min.

25 The retention time for the complex ¹⁷⁷Lu-DO3A-HPE was
14.5 min, and the radiolabeling yield was ~80%.

Example III. Synthesis of 1,4,7,10-tetraazacyclododecane-1-[N-(phthalimide)ethyl]-4,7,10-triacetic acid (DO3A-EP).



5
To a solution of tributyl ester of DO3A (160 mg, 0.312 mmole) in anhydrous acetonitrile (50 mL) were added N(2-bromoethyl)phthalimide (68 mg, 0.342 mmole) and triethylamine (20 mg, 0.67 mmole). The resulting mixture was stirred at room temperature for 48 hours. Solvents were removed under the reduced pressure. The residue was extracted with dichloromethane (2X50 mL), washed with water (2X30 mL), dried over anhydrous sodium sulfate. After removal of solvent, the residue was dissolved in a mixture of dichloromethane (15 mL) and anhydrous TFA (15 mL). The mixture was stirred at room temperature overnight. Solvents were removed under reduced pressure. To the residue was added water (3-5 mL) and the resulting mixture was filtered. The filtrate was concentrate to ~2 mL, and the crude product was purified by HPLC with the following method:

Solvent A: 0.1% TFA
Solvent B: acetonitrile
25 Column: Zorbax C18 reversed phase semi-prep column

Flow rate: 3 mL/min

Gradient: Solvent B from 5% to 20% over 20 min.

The fractions at retention times of 10 - 12.5 min were collected. The collected fractions were combined.

- 5 Solvents were removed on a rotary evaporator. The residue was dissolved in 1 mL of water, and was re-purified using a slightly different gradient: Solvent B was isocratic (5%) for the first 5 minutes, and then went from 5% to 20% over the next 15 min. The fractions
10 at 13-17 min were collected. The collected fractions were combined, and lyophilized to give a white powder. The yield was 15 mg. LC-MS: $M/z = 520.5$ for $[C_{24}H_{34}N_5O_8]^+$, 261.2 for $[C_{24}H_{35}N_5O_8]^{2+}$.

15 **Example IV. Synthesis of ^{111}In complex of DO3A-EP.**

- To a clean 5 mL vial containing 0.6 mL of DO3A-EP solution (200 $\mu\text{g/mL}$ in 0.5 M NH_4OAc , pH = 7.5) was added 50 μL of $^{111}\text{InCl}_3$ solution (~0.5 mCi) in 0.05 N HCl. The reaction mixture was heated at 50 $^\circ\text{C}$ for 15 min. After
20 cooling to room temperature, the resulting solution was analyzed by an ITLC method using Gelman Sciences silicon gel paper strip, and a 50:50 mixture of saline and acetone as mobile phase. Using this method, $^{111}\text{InCl}_3$ and $[^{111}\text{In}]\text{acetate}$ remain at the origin while the
25 radiolabeled DO3A-EP migrates to the solvent front. The yield was 85%.

Example V. Synthesis of ^{177}Lu complex of DO3A-EP.

To a clean 5 mL vial containing 0.6 mL of DO3A-EP solution (200 $\mu\text{g/mL}$ in 0.5 M NH_4OAc , pH = 7.5) was added
 5 5 μL of $^{177}\text{LuCl}_3$ solution (~4 mCi) in 0.05 N HCl. The reaction mixture was heated at 50 °C for 15 min. After cooling to room temperature, the resulting solution was analyzed by an HPLC method. The retention time was 19 min and the radiolabeling yield was 85%.

10 HP-1100 HPLC System

Detector: IN-US β -Detector

Column: Zorbax C_{18} reverse phase column (25 cm x 4.6 mm)

Flow Rate: 1.0 mL/min

15 Solvent A: 25 mM ammonium acetate buffer (pH 6.8)

Solvent B: 100 % CH_3CN

Gradient: Time (min)	0	18	19	25	26	32
%B	0	20	60	60	0	0
%A	100	80	40	40	100	100

20

Example IV. Synthesis of ^{90}Y complex of DO3A-EP.

To a clean 5 mL vial containing 0.6 mL of DO3A-EP solution (200 $\mu\text{g/mL}$ in 0.5 M NH_4OAc , pH = 7.5) was added
 25 5 μL of $^{90}\text{YCl}_3$ solution (~3 mCi) in 0.05 N HCl. The reaction mixture was heated at 50 °C for 15 min. After cooling to room temperature, the resulting solution was

analyzed by an HPLC method. The retention time was 19.2 min and the radiolabeling yield was 83%.

HP-1100 HPLC System

Detector: IN-US β -Detector

5 Column: Zorbax C₁₈ reverse phase column (25 cm x 4.6 mm)

Flow Rate: 1.0 mL/min

Solvent A: 25 mM ammonium acetate buffer (pH 6.8)

Solvent B: 100 % CH₃CN

10	Gradient: Time (min)	0	18	19	25	26	32
	%B	0	20	60	60	0	0
	%A	100	80	40	40	100	100

Utility

The diagnostic radiopharmaceuticals are
 15 administered by intravenous injection, usually in saline solution, at a dose of 1 to 100 mCi per 70 kg body weight, or preferably at a dose of 5 to 50 mCi. Imaging is performed using known procedures.

The therapeutic radiopharmaceuticals are
 20 administered by intravenous injection, usually in saline solution, at a dose of 0.1 to 100 mCi per 70 kg body weight, or preferably at a dose of 0.5 to 5 mCi per 70 kg body weight.

The magnetic resonance imaging contrast agents of
 25 the present invention may be used in a similar manner as other MRI agents as described in U.S. Patent 5,155,215; U.S. Patent No. 5,087,440; Margerstadt et al., Magn. Reson. Med., 1986, 3, 808; Runge et al., Radiology, 1988, 166, 835; and Bousquet et al., Radiology, 1988,

166, 693. Generally, sterile aqueous solutions of the contrast agents are administered to a patient intravenously in dosages ranging from 0.01 to 1.0 mmoles per kg body weight.

5 For use as X-ray contrast agents, the compositions of the present invention should generally have a heavy atom concentration of 1 mM to 5 M, preferably 0.1 M to 2 M. Dosages, administered by intravenous injection, will typically range from 0.5 mmol/kg to 1.5 mmol/kg,
10 preferably 0.8 mmol/kg to 1.2 mmol/kg. Imaging is performed using known techniques, preferably X-ray computed tomography.

The pharmaceuticals of the present invention are useful for imaging hypoxia, apoptosis, cardiac ischemia, thrombosis, infection, inflammation, cancer, restenosis,
15 atherosclerosis, diabetic retinopathy, macular degeneration, wound healing, and reperfusion injury, in a patient. The imaging radiopharmaceuticals of the present invention comprised of a gamma ray or positron
20 emitting isotope. The radiopharmaceuticals of the present invention comprised of a beta, alpha or Auger electron emitting isotope are useful for treatment of pathological processes including cancer, rstenosis, diabetic retinopathy, and macular degeneration, by
25 delivering a cytotoxic dose of radiation to the locus of expression of the receptor or enzyme with which the BM interacts (targets). The treatment of cancer is affected by the systemic administration of the radiopharmaceuticals resulting in a cytotoxic radiation
30 dose to tumors.

The compounds of the present invention comprised of one or more paramagnetic metal ions selected from

gadolinium, dysprosium, iron, and manganese, are useful as contrast agents for magnetic resonance imaging (MRI) of hypoxia, apoptosis, cardiac ischemia, thrombosis, infection, inflammation, cancer, restenosis, atherosclerosis, diabetic retinopathy, macular degeneration, wound healing, and reperfusion injury.

The compounds of the present invention comprised of one or more heavy atoms with atomic number of 20 or greater are useful as X-ray contrast agents for X-ray imaging of hypoxia, apoptosis, cardiac ischemia, thrombosis, infection, inflammation, cancer, restenosis, atherosclerosis, diabetic retinopathy, macular degeneration, wound healing, and reperfusion injury.

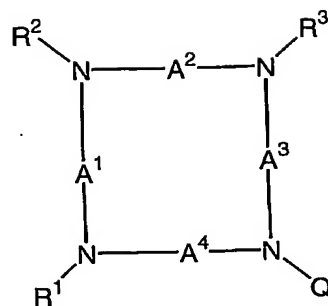
Biochemical assays and in vivo models for testing the pharmaceuticals of the present invention are described in U.S. Patent No. 5,879,657, PCT Application WO 98/15295, and PCT Application WO 99/51628.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

All publications, patents, and patent documents are incorporated by reference herein, in their entirety, as though individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of formula:



5 or pharmaceutically acceptable salts thereof,

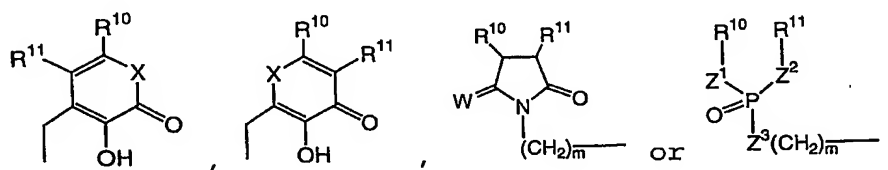
wherein:

R^1 , R^2 , and R^3 are independently selected from: C_1 - C_{10} alkyl substituted with 1-5 R^4 , C_1 - C_{10} fluoroalkyl substituted with 1-5 R^4 , C_2 - C_{10} alkenyl substituted with 1-5 R^4 , C_2 - C_{10} fluoroalkenyl substituted with 1-5 R^4 , and aryl substituted with 1-5 R^4 , fluoroaryl substituted with 1-5 R^4 ;

R^4 is independently selected at each occurrence from: $C(=O)R^5$, $S(O)_2OR^5$, $C(=O)OR^5$, $C(=O)NR^6R^7$, $PO(OR^6)(OR^7)$;

15 R^5 , R^6 and R^7 are independently selected from: H, C_1 - C_{10} alkyl substituted with 0-5 R^8 , C_2 - C_{10} alkenyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^8 , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , and fluoroaryl substituted with 0-3 R^8 ,
20 said C_1 - C_{10} alkyl and C_2 - C_{10} alkenyl groups optionally interrupted with -O-, -S-, -NH-, -S(O)-, -S(O)₂-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, or -NHC(S)NH-;

- or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally interrupted with -O-, -S-, -NR⁹-, -S(O)-, -S(O)₂-, -P(O)(OR⁹)-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, or -NHC(S)NH-;
- 10 R^8 is independently selected at each occurrence from: H, -OH, -NHR⁹, -C(=O)R⁹, -OC(=O)R⁹, -OC(=O)OR⁹, -C(=O)OR⁹, -C(=O)N(R⁹)₂, -PO(OR⁹)₂, -SR⁹, -SOR⁹, -SO₂R⁹, -NHC(=O)R⁹, -NHC(=O)NHR⁹, -CH₂OR⁹, and -NHC(=S)NHR⁹;
- R^9 is independently selected at each occurrence from: H,
- 15 C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkenyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;
- A^1 , A^2 , A^3 , and A^4 are independently -(CR⁵R⁵)_n-, wherein n is 2 or 3.
- 20 Q is a functional group selected from:



- wherein R^{10} and R^{11} are independently selected at each
- 25 occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl

substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^{12} , and aryl substituted with 0-5 R^{12} ,

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

m is 1-3;

10 W is selected from two hydrogen atoms or O;

R^{12} is independently selected at each occurrence from the group: COR^{13} , $C(=O)OR^{13}$, $C(=O)N(R^{13})_2$, $PO(OR^{13})_2$, OR^{13} , and SO_2OR^{13} ;

15 R^{13} is independently selected at each occurrence from the group: H, and C_1 - C_6 alkyl;

X is selected from O or NR^5 ; and

Z^1 , Z^2 , and Z^3 are independently selected from: O, NH , CH_2NH , and a direct bond.

20 2. A compound of claim 1, wherein:

R^1 , R^2 , and R^3 are independently selected from: C_1 - C_3 alkyl substituted with 1-2 R^4 , C_1 - C_3 fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;

25 R^5 , R^6 and R^7 are independently selected from: H, C_1 - C_3 alkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_1 - C_3 fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;

or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkenyl substituted with 0-2 R^8 , or an aryl substituted with 0-2 R^8 ;

5 R^9 is independently selected at each occurrence from: H, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkenyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

10 A^1 , A^2 , A^3 , and A^4 are $-(CR^5R^5)_2-$;

R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_3 alkyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkyl substituted with 0-2 R^{12} , C_1 - C_3 fluoroalkyl substituted with 0-2 R^{12} , C_2 - C_3 alkenyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkenyl substituted with 0-2 R^{12} , C_2 - C_3 fluoroalkenyl substituted with 0-2 R^{12} , and aryl substituted with 0-2 R^{12} ;

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl group substituted with 0-2 R^{12} , or aryl group substituted with 0-2 R^{12} ;

R^{13} is H or C_1 - C_3 alkyl; and

Z^1 , Z^2 , and Z^3 are independently selected from: O, NH, and a direct bond.

25

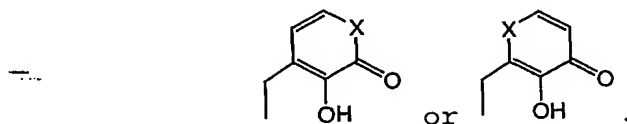
3. A compound of claim 1 or 2, wherein:

R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from: COOH, PO_3H_2 , SO_3H , and $C(=O)NR^6R^7$;

A^1 , A^2 , and A^3 are $-(CH_2)_2-$; and

Q is a functional group of the formula:



5

4. A compound of claim 1 or 2, wherein:

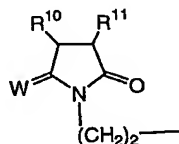
R^1 , R^2 , and R^3 are $-CH_2R^4$;

R^4 is independently elected at each occurrence from:

$COOH$, PO_3H_2 , SO_3H , and $C(=O)NR^6R^7$;

10 A^1 , A^2 , A^3 and A^4 are $-(CH_2)_2-$; and

Q is a functional group of the formula:



15 wherein R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

5. A compound of claim 1 or 2, wherein:

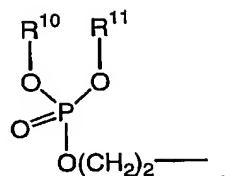
R^1 , R^2 , and R^3 are $-CH_2R^4$;

20 R^4 is independently elected at each occurrence from:

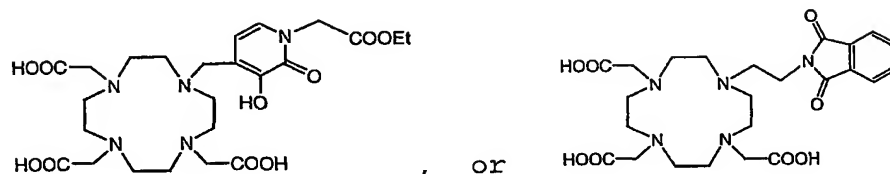
$COOH$, PO_3H_2 , SO_3H , and $C(=O)NR^6R^7$;

A^1 , A^2 , A^3 , and A^4 are $-(CH_2)_2-$; and

Q is a functional group of the formula:



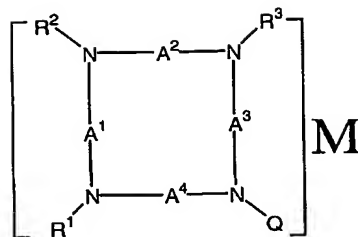
5 6. A compound of claim 1 or 2 of the formula:



7. A metal chelate complex comprising a compound
 10 according to any one of claims 1 to 6 complexed to a
 metal ion of atomic number 21-31, 39-49, 50, 56-80, 82,
 83, 90.

8. A metal chelate complex comprising a compound
 15 according to any one of claims 1 to 6 complexed to a
 radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga ,
 ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb ,
 ^{177}Lu , ^{186}Re , and ^{188}Re .

20 9. A metal chelate complex according to claim 7 or 8
 of the formula:



or pharmaceutically acceptable salts thereof,

wherein:

- 5 M is X or X¹;

wherein:

X is a radionuclide selected from: ⁶⁴Cu, ⁶²Cu, ⁶⁰Cu, ⁶⁷Cu, ⁶⁷Ga, ⁶⁸Ga, ^{99m}Tc, ¹¹¹In, ⁹⁰Y, ¹⁴⁹Pr, ¹⁵³Sm, ¹⁵⁹Gd, ¹⁶⁶Ho, ¹⁶⁹Yb, ¹⁷⁷Lu, ¹⁸⁶Re, and ¹⁸⁸Re;

- 10 X¹ is a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90;

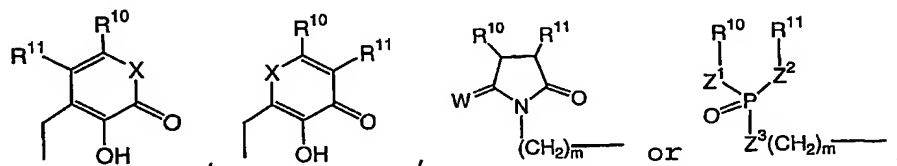
wherein:

- R¹, R², and R³ are independently selected from: C₁-C₁₀ alkyl substituted with 1-5 R⁴, C₁-C₁₀ fluoroalkyl substituted with 1-5 R⁴, C₂-C₁₀ alkenyl substituted with 1-5 R⁴, C₂-C₁₀ fluoroalkenyl substituted with 1-5 R⁴, and aryl substituted with 1-5 R⁴, fluoroaryl substituted with 1-5 R⁴;

- R⁴ is independently selected at each occurrence from: - C(=O)R⁵, -S(O)₂OR⁵, -C(=O)OR⁵, -C(=O)NR⁶R⁷, -PO(OR⁶)(OR⁷);

- R⁵, R⁶ and R⁷ are independently selected from: H, C₁-C₁₀ alkyl substituted with 0-5 R⁸, C₂-C₁₀ alkenyl substituted with 0-5 R⁸, C₃-C₁₀ cycloalkyl substituted with 0-5 R⁸, C₁-C₁₀ fluoroalkyl substituted with 0-5 R⁸, C₂-C₁₀ fluoroalkenyl substituted with 0-5 R⁸, aryl substituted

- with 0-5 R^8 , and fluoroaryl substituted with 0-3 R^8 ,
 said C_1 - C_{10} alkyl and C_2 - C_{10} alkenyl groups optionally
 interrupted with -O-, -S-, -NH-, -S(O)-, -S(O)₂-, -
 P(O)(OR⁹)O-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -
 5 NHC(O)NH-, -NHC(S)NH-;
 or alternatively, R^6 and R^7 may be taken together, with
 the atoms through which they are attached, to form a C_3 -
 C_{10} cycloalkyl substituted with 0-5 R^8 , C_3 - C_{10}
 cycloalkenyl substituted with 0-5 R^8 , aryl substituted
 10 with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said
 C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally
 interrupted with -O-, -S-, -NR⁹-, -S(O)-, -S(O)₂-, -
 P(O)(OR⁹)-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)-, -P(O)(NHR⁹)O-, -
 C(O)NH-, -NHC(O)-, -NHC(O)NH-, or -NHC(S)NH-;
 15 R^8 is independently selected at each occurrence from: H,
 OH, NHR⁹, C(=O)R⁹, OC(=O)R⁹, OC(=O)OR⁹, C(=O)OR⁹,
 C(=O)N(R⁹)₂, PO(OR⁹)₂, SR⁹, SOR⁹, SO₂R⁹, NHC(=O)R⁹,
 NHC(=O)NHR⁹, CH₂OR⁹, and NHC(=S)NHR⁹;
 R^9 is independently selected at each occurrence from: H,
 20 C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6
 alkenyl, C_3 - C_6 cycloalkenyl, C_1 - C_6 fluoroalkenyl, benzyl,
 fluorobenzyl, phenyl, and fluorophenyl;
 A^1 , A^2 , A^3 , and A^4 are independently $-(CR^5R^5)_n-$, wherein n
 is 2 or 3.
 25 Q is a functional group selected from:



wherein R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^{12} , and aryl substituted with 0-5 R^{12} ,

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

m is 1-3;

W is selected from two hydrogen atoms or O;

R^{12} is independently selected at each occurrence from the group: $-\text{COR}^{13}$, $-\text{C}(=\text{O})\text{OR}^{13}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{13})_2$, $-\text{PO}(\text{OR}^{13})_2$, $-\text{OR}^{13}$, and $-\text{SO}_2\text{OR}^{13}$;

R^{13} is independently selected at each occurrence from the group: H, and C_1 - C_6 alkyl;

X is selected from $-\text{O}-$ or $-\text{NR}^5-$; and

Z^1 , Z^2 , and Z^3 are independently selected from: $-\text{O}-$, $-\text{NH}-$, $-\text{CH}_2\text{NH}-$, and a direct bond.

10. A metal chelate complex of claim 9, wherein:

R^1 , R^2 , and R^3 are independently selected from: C_1 - C_3 alkyl substituted with 1-2 R^4 , C_1 - C_3 fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;

- R^5 , R^6 and R^7 are independently selected from: H, C_1 - C_3 alkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_1 - C_3 fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;
- 5 or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkenyl substituted with 0-2 R^8 , or an aryl substituted with 0-2 R^8 ;
- 10 R^9 is independently selected at each occurrence from: H, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;
- A^1 , A^2 , A^3 , and A^4 are $-(CR^5R^5)_2-$;
- 15 R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_3 alkyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkyl substituted with 0-2 R^{12} , C_1 - C_3 fluoroalkyl substituted with 0-2 R^{12} , C_2 - C_3 alkenyl substituted with 0-2 R^{12} , C_3 - C_6 cycloalkenyl substituted with 0-2 R^{12} , C_2 -
- 20 C_3 fluoroalkenyl substituted with 0-2 R^{12} , and aryl substituted with 0-2 R^{12} ,
- or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl group substituted with 0-2 R^{12} , or
- 25 aryl group substituted with 0-2 R^{12} ;
- R^{13} is H or C_1 - C_3 alkyl; and
- Z^1 , Z^2 , and Z^3 are independently selected from: O, NH, and a direct bond.

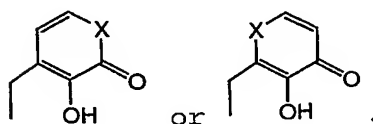
- 30 11. A metal chelate complex of claim 9 or 10, wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: $-\text{COOH}$, $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

5 Q is a functional group of the formula:



12. A metal chelate complex of claim 9 or 10, wherein:

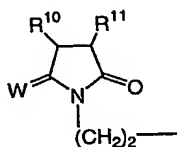
10 R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: $-\text{COOH}$, $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:

15



wherein R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

20 13. A metal chelate complex of claim 9 or 10, wherein:

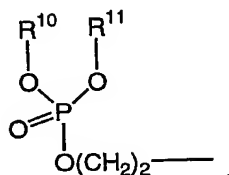
R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from:
 COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

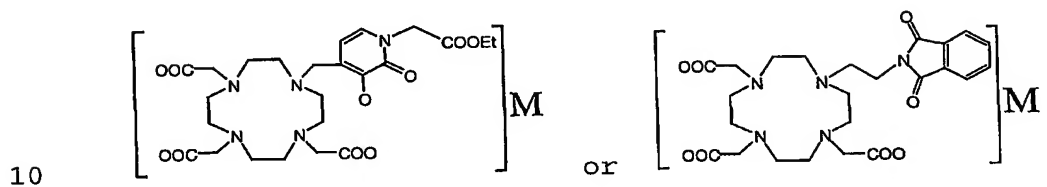
A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:

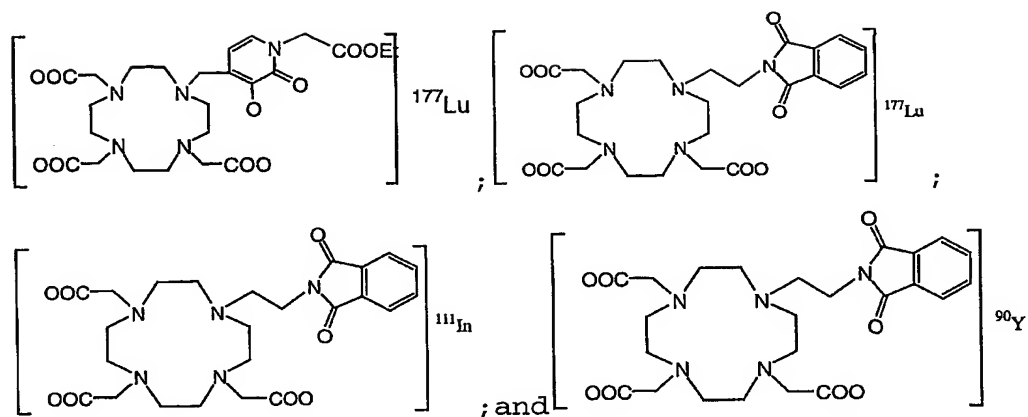
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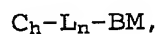
14. A metal chelate complex of claim 9 or 10 that is:



15. A metal chelate complex of claim 9 or 10 selected from the group consisting of:



5 16. A novel conjugate of the formula:

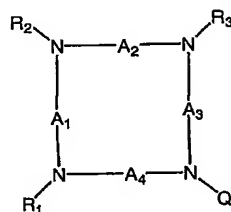


or pharmaceutically acceptable salts thereof,

wherein,

C_h is a chelator of formula:

10



wherein:

15 R¹, R², and R³ are independently selected from: C₁-C₁₀
alkyl substituted with 1-5 R⁴, C₁-C₁₀ fluoroalkyl
substituted with 1-5 R⁴, C₂-C₁₀ alkenyl substituted with
1-5 R⁴, C₂-C₁₀ fluoroalkenyl substituted with 1-5 R⁴, and

aryl substituted with 1-5 R^4 , fluoroaryl substituted with 1-5 R^4 ;

R^4 is independently selected at each occurrence from: $C(=O)R^5$, $S(O)_2OR^5$, $C(=O)OR^5$, $C(=O)NR^6R^7$, $PO(OR^6)(OR^7)$;

- 5 R^5 , R^6 and R^7 are independently selected from: H, a direct bond to L_n , C_1 - C_{10} alkyl substituted with 0-5 R^8 , C_2 - C_{10} alkenyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^8 , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , and fluoroaryl substituted with 0-3 R^8 , said C_1 - C_{10} alkyl and C_2 - C_{10} alkenyl groups optionally interrupted with O, S, NH, $S(O)$, $S(O)_2$, $P(O)(OR^9)O$, $P(O)(NHR^9)O$, $C(O)NH$, $NHC(O)$, $NHC(O)NH$, $NHC(S)NH$;

- 15 or alternatively, R^6 and R^7 may be taken together, with the atoms through which they are attached, to form a C_3 - C_{10} cycloalkyl substituted with 0-5 R^8 , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally interrupted with $-O-$, $-S-$, $-NR^9-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR^9)-$, $-P(O)(OR^9)O-$, $-P(O)(NHR^9)-$, $-P(O)(NHR^9)O-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, or $-NHC(S)NH-$;

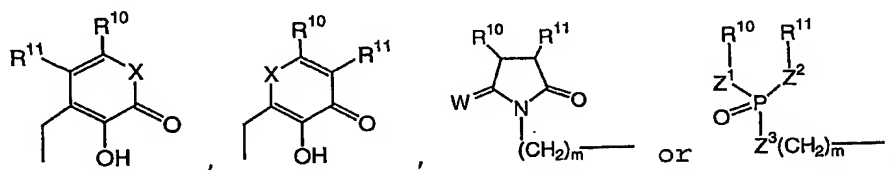
- R^8 is independently selected at each occurrence from: -
 25 H, $-OH$, $-NHR^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-PO(OR^9)_2$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-NHC(=O)R^9$, $-NHC(=O)NHR^9$, $-CH_2OR^9$, $-NHC(=S)NHR^9$, and a direct bond to L_n ;

- R^9 is independently selected at each occurrence from: H,
 30 C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkenyl, benzyl,

fluorobenzyl, phenyl, fluorophenyl, and a direct bond to L_n ;

A^1 , A^2 , A^3 , and A^4 are independently $-(CR^5R^5)_n-$, wherein n is 2 or 3.

5 Q is a functional group selected from:



wherein:

10 R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 -
15 C_{10} fluoroalkenyl substituted with 0-5 R^{12} , aryl substituted with 0-5 R^{12} , and a direct bond to L_n ;

or, alternatively, R^{10} and R^{11} may be taken together with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 -
20 C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

m is 1-3;

W is selected from two hydrogen atoms or O;

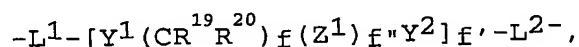
R^{12} is independently selected at each occurrence from
25 the group: $-COR^{13}$, $-C(=O)OR^{13}$, $-C(=O)N(R^{13})_2$, $-PO(OR^{13})_2$, $-OR^{13}$, $-SO_2OR^{13}$, and a direct bond to L_n ;

R^{13} is independently selected at each occurrence from the group: H, C_1-C_6 alkyl, and a direct bond to L_n ;

X is selected from O or NR^5 ;

Z^1 , Z^2 , and Z^3 are independently selected at each
5 occurrence from: O, NH, CH_2NH , and a direct bond;

L_n is a linking group of formula:



10 L^1 is $-(CH_2)_gZ^1]_{g'}-(CR^{19}R^{20})_{g''}-$;

L^2 is $-(CR^{19}R^{20})_{g''}-[Z^1(CH_2)_g]_{g'}-$;

g is independently 0-10;

g' is independently 0-1;

g'' is independently 0-10;

15 f is independently 0-10;

f' is independently 0-10;

f'' is independently 0-1;

Y^1 and Y^2 are independently selected, at each occurrence, from: a direct bond, $-O-$, $-NR^{20}-$, $-C(=O)-$, $-$

20 $C(=O)O-$, $-OC(=O)O-$, $-C(=O)NH-$, $-C(=NR^{20})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-NHC(=O)-$, $-(NH)_2C(=O)-$, and $-(NH)_2C(=S)-$;

R^{19} and R^{20} are independently selected at each occurrence from: H, a direct bond to BM, C_1-C_{10} alkyl substituted

with 0-5 R^{21} , and alkaryl wherein the aryl is

25 substituted with 0-5 R^{21} ;

R^{21} is independently selected at each occurrence from the group: $-NHR^{22}$, $-C(=O)R^{22}$, $-OC(=O)R^{22}$, $-OC(=O)OR^{22}$, $-C(=O)OR^{22}$, $-C(=O)NR_2^{22}$, $-CN$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-NHC(=O)R^{22}$, $-NHC(=O)NHR^{22}$, $-NHC(=S)NHR^{22}$, and a direct
5 bond to BM;

R^{22} is independently selected at each occurrence from the group: H, C_1 - C_6 alkyl, benzyl, phenyl, and a direct bond to BM; and

BM is a biologically active targeting molecule selected
10 from the group: IIb/IIIa receptor ligands, fibrin binding peptides, leukocyte binding peptides, chemotactic peptides, LTB_4 receptor antagonists, somatostatin analogs, selectin binding peptides, vitronectin receptor antagonists, growth factor receptor
15 antagonists, tyrosine kinase inhibitors, matrix metalloproteinase inhibitors, oligonucleotides, fatty acids, nitroimidazoles, and carbohydrates.

17. A conjugate of claim 16, wherein,

20 R^1 , R^2 , and R^3 are independently selected from: C_1 - C_3 alkyl substituted with 1-2 R^4 , C_1 - C_3 fluoroalkyl substituted with 1-2 R^4 , aryl substituted with 1-2 R^4 , and fluoroaryl substituted with 1-2 R^4 ;

R^5 , R^6 and R^7 are independently selected from: H, a
25 direct bond to L_n , C_1 - C_3 alkyl substituted with 0-2 R^8 , C_3 - C_6 cycloalkyl substituted with 0-2 R^8 , C_1 - C_3 fluoroalkyl substituted with 0-2 R^8 , and aryl substituted with 0-2 R^8 ;

or alternatively, R^6 and R^7 may be taken together, with
30 the atoms through which they are attached, to form a C_3 -

C₆ cycloalkyl substituted with 0-2 R⁸, C₃-C₆ cycloalkenyl substituted with 0-2 R⁸, or aryl substituted with 0-2 R⁸;

R⁹ is independently selected at each occurrence from: H,
5 a direct bond to L_n, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkyl, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₁-C₆ fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and fluorophenyl;

A¹, A², A³, and A⁴ are -(CR⁵R⁵)₂-;

10 R¹⁰ and R¹¹ are independently selected at each occurrence from: H, a direct bond to L_n, C₁-C₃ alkyl substituted with 0-2 R¹², C₃-C₆ cycloalkyl substituted with 0-2 R¹², C₁-C₃ fluoroalkyl substituted with 0-2 R¹², C₂-C₃ alkenyl substituted with 0-2 R¹², C₃-C₆ cycloalkenyl substituted
15 with 0-2 R¹², C₂-C₃ fluoroalkenyl substituted with 0-2 R¹², and aryl substituted with 0-2 R¹²,

or, alternatively, R¹⁰ and R¹¹ may be taken together to form a C₃-C₁₀ cycloalkyl group substituted with 0-2 R¹², or ortho-aryl group substituted with 0-2 R¹²;

20 R¹³ is H or C₁-C₃ alkyl; and

Z¹, Z², and Z³ are independently selected from: O, NH, and a direct bond.

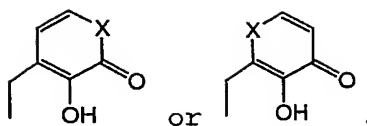
18. A conjugate of claim 16 or 17, wherein:

25 R¹, R², and R³ are -CH₂R⁴;

R⁴ is independently elected at each occurrence from: -COOH, -PO₃H₂, -SO₃H, and -C(=O)NR⁶R⁷;

A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:



19. A conjugate of claim 16 or 17, wherein:

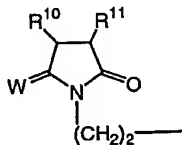
5 R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from:
 COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:

10



wherein:

R^{10} and R^{11} are taken together to form a phenyl group
substituted with 0-2 R^{12} .

15

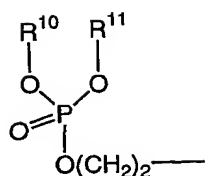
20. A conjugate of claim 16 or 17, wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from: -
 COOH , $-\text{PO}_3\text{H}_2$, $-\text{SO}_3\text{H}$, and $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

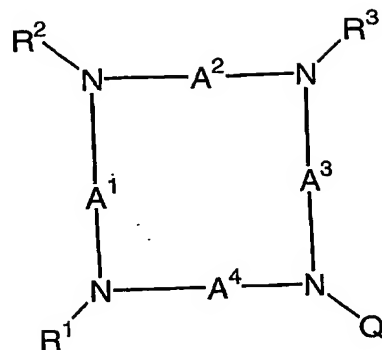
20 A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

Q is a functional group of the formula:



21. A novel metallopharmaceutical comprising a conjugate according to any one of claims 16 to 20
- 5 chelated with a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re .
22. A novel metallopharmaceutical comprising a conjugate
- 10 according to any one of claims 16 to 20 chelated with a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.
23. A novel metallopharmaceutical according to claim 21
- 15 or 22 of the formula:
- $$\text{M}-\text{C}_h-\text{L}_n-\text{BM},$$
- or pharmaceutically acceptable salts thereof,
- wherein:
- M is X or X^1 ;
- 20 wherein:
- X is a radionuclide selected from: ^{64}Cu , ^{62}Cu , ^{60}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{90}Y , ^{149}Pr , ^{153}Sm , ^{159}Gd , ^{166}Ho , ^{169}Yb , ^{177}Lu , ^{186}Re , and ^{188}Re ;
- X^1 is a metal ion of atomic number 21-31, 39-49, 50, 56-
- 25 80, 82, 83, 90;

C_h is a chelator of formula:



wherein:

- R¹, R², and R³ are independently selected from: C₁-C₁₀ alkyl substituted with 1-5 R⁴, C₁-C₁₀ fluoroalkyl substituted with 1-5 R⁴, C₂-C₁₀ alkenyl substituted with 1-5 R⁴, C₂-C₁₀ fluoroalkenyl substituted with 1-5 R⁴, and aryl substituted with 1-5 R⁴, fluoroaryl substituted with 1-5 R⁴;
- 10 R⁴ is independently selected at each occurrence from: C(=O)R⁵, S(O)₂OR⁵, C(=O)OR⁵, C(=O)NR⁶R⁷, PO(OR⁶)(OR⁷);
- R⁵, R⁶ and R⁷ are independently selected from: H, a direct bond to L_n, C₁-C₁₀ alkyl substituted with 0-5 R⁸, C₂-C₁₀ alkenyl substituted with 0-5 R⁸, C₃-C₁₀ cycloalkyl substituted with 0-5 R⁸, C₁-C₁₀ fluoroalkyl substituted with 0-5 R⁸, C₂-C₁₀ fluoroalkenyl substituted with 0-5 R⁸, aryl substituted with 0-5 R⁸, and fluoroaryl substituted with 0-3 R⁸, said C₁-C₁₀ alkyl and C₂-C₁₀ alkenyl groups optionally interrupted with -O-, -S-, -
- 15 NH-, -S(O)-, -S(O)₂-, -P(O)(OR⁹)O-, -P(O)(NHR⁹)O-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -NHC(S)NH-;
- 20 or alternatively, R⁶ and R⁷ may be taken together, with the atoms through which they are attached, to form a C₃-C₁₀ cycloalkyl substituted with 0-5 R⁸, C₃-C₁₀

- cycloalkenyl substituted with 0-5 R^8 , aryl substituted with 0-5 R^8 , or fluoroaryl substituted with 0-5 R^8 ; said C_3 - C_{10} alkyl and C_3 - C_{10} cycloalkenyl groups optionally interrupted with O, S, NR^9 , $S(O)$, $S(O)_2$, $P(O)(OR^9)$,
 5 $P(O)(OR^9)O$, $P(O)(NHR^9)$, $P(O)(NHR^9)O$, $C(O)NH$, $NHC(O)$, $NHC(O)NH$, $NHC(S)NH$;

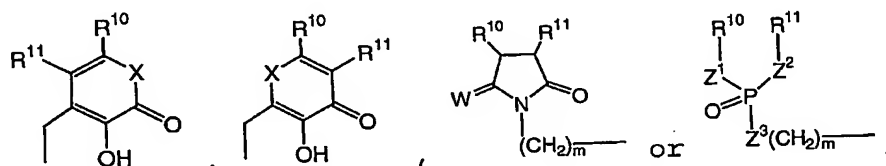
- R^8 is independently selected at each occurrence from: H, OH, NHR^9 , $C(=O)R^9$, $OC(=O)R^9$, $OC(=O)OR^9$, $C(=O)OR^9$, $C(=O)N(R^9)_2$, $PO(OR^9)_2$, SR^9 , SOR^9 , SO_2R^9 , $NHC(=O)R^9$,
 10 $NHC(=O)NHR^9$, CH_2OR^9 , $NHC(=S)NHR^9$, and a direct bond to L_n ;

- R^9 is independently selected at each occurrence from: H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 alkenyl, C_3 - C_6 cycloalkenyl, C_1 - C_6 fluoroalkenyl, benzyl, fluorobenzyl, phenyl, fluorophenyl, and a direct bond to
 15 L_n ;

A^1 , A^2 , A^3 , and A^4 are independently $-(CR^5R^5)_n-$, wherein n is 2 or 3.

Q is a functional group selected from:

20



wherein:

- R^{10} and R^{11} are independently selected at each occurrence from: H, C_1 - C_{10} alkyl substituted with 0-5 R^{12} , C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , C_1 - C_{10} fluoroalkyl substituted with 0-5 R^{12} , C_2 - C_{10} alkenyl substituted with
 25

0-5 R^{12} , C_3 - C_{10} cycloalkenyl substituted with 0-5 R^{12} , C_2 - C_{10} fluoroalkenyl substituted with 0-5 R^{12} , aryl substituted with 0-5 R^{12} , and a direct bond to L_n ;

or, alternatively, R^{10} and R^{11} may be taken together, with the atoms through which they are attached, to form a cyclic ring system, said ring system selected from: C_3 - C_{10} cycloalkyl substituted with 0-5 R^{12} , and aryl substituted with 0-3 R^{12} ;

m is 1-3;

10 W is selected from two hydrogen atoms or O;

R^{12} is independently selected at each occurrence from the group: COR^{13} , $C(=O)OR^{13}$, $C(=O)N(R^{13})_2$, $PO(OR^{13})_2$, OR^{13} , SO_2OR^{13} , and a direct bond to L_n ;

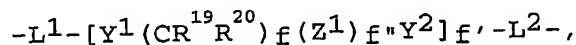
R^{13} is independently selected at each occurrence from the group: H, C_1 - C_6 alkyl, and a direct bond to L_n ;

X is selected from O or NR^5 ;

Z^1 , Z^2 , and Z^3 are independently selected at each occurrence from: O, NH, CH_2NH , and a direct bond;

L_n is a linking group of formula:

20



L^1 is $-[(CH_2)_gZ^1]_{g'}-(CR^{19}R^{20})_{g''}-$;

L^2 is $-(CR^{19}R^{20})_{g''}-[Z^1(CH_2)_g]_{g'}-$;

25 g is independently 0-10;

g' is independently 0-1;

g'' is independently 0-10;

f is independently 0-10;

f' is independently 0-10;

f" is independently 0-1;

Y^1 and Y^2 are independently selected at each occurrence

5 from: a direct bond, -O-, $-NR^{20}-$, -C=O-, -C(=O)O-, -
OC(=O)O-, -C(=O)NH-, -C(=NR²⁰)-, -S-, -S(O)-, -S(O)₂-, -
NHC(=O)-, -(NH)₂C(=O)-, and -(NH)₂(C=S)-;

R^{19} and R^{20} are independently selected at each occurrence

10 from: H, a direct bond to BM, C₁-C₁₀ alkyl substituted
with 0-5 R^{21} , and alkaryl wherein the aryl is
substituted with 0-5 R^{21} ;

R^{21} is independently selected at each occurrence from

the group: $-NHR^{22}$, $-C(=O)R^{22}$, $-OC(=O)R^{22}$, $-OC(=O)OR^{22}$, -
C(=O)OR²², -C(=O)NR²², -CN, -SR²², -S(O)R²², -S(O)₂R²², -
15 NHC(=O)R²², -NHC(=O)NHR²², -NHC(=S)NHR²², and a direct
bond to BM;

R^{22} is independently selected at each occurrence from
the group: H, C₁-C₆ alkyl, benzyl, phenyl, and a direct
bond to BM; and

20 BM is a biologically active targeting molecule selected
from the group: IIb/IIIa receptor ligands, fibrin
binding peptides, leukocyte binding peptides,
chemotactic peptides, LTB₄ receptor antagonists,
somatostatin analogs, selectin binding peptides,
25 vitronectin receptor antagonists, growth factor receptor
antagonists, tyrosine kinase inhibitors, matrix
metalloproteinase inhibitors, oligonucleotides, fatty
acids, nitroimidazoles, and carbohydrates.

24. A metallopharmaceutical of claim 23, wherein,
R¹, R², and R³ are independently selected from: C₁-C₃
alkyl substituted with 1-2 R⁴, C₁-C₃ fluoroalkyl
substituted with 1-2 R⁴, aryl substituted with 1-2 R⁴,
5 and fluoroaryl substituted with 1-2 R⁴;
R⁵, R⁶ and R⁷ are independently selected from: H, a
direct bond to L_n, C₁-C₃ alkyl substituted with 0-2 R⁸,
C₃-C₆ cycloalkyl substituted with 0-2 R⁸, C₁-C₃
fluoroalkyl substituted with 0-2 R⁸, and aryl
10 substituted with 0-2 R⁸;
or alternatively, R⁶ and R⁷ may be taken together, with
the atoms through which they are attached, to form a C₃-
C₆ cycloalkyl substituted with 0-2 R⁸, C₃-C₆ cycloalkenyl
substituted with 0-2 R⁸, or aryl substituted with 0-2
15 R⁸;
R⁹ is independently selected at each occurrence from: H,
a direct bond to L_n, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₆
fluoroalkyl, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₁-C₆
fluoroalkenyl, benzyl, fluorobenzyl, phenyl, and
20 fluorophenyl;
A¹, A², A³, and A⁴ are -(CR⁵R⁵)₂-;
R¹⁰ and R¹¹ are independently selected at each occurrence
from: H, a direct bond to L_n, C₁-C₃ alkyl substituted
with 0-2 R¹², C₃-C₆ cycloalkyl substituted with 0-2 R¹²,
25 C₁-C₃ fluoroalkyl substituted with 0-2 R¹², C₂-C₃ alkenyl
substituted with 0-2 R¹², C₃-C₆ cycloalkenyl substituted
with 0-2 R¹², C₂-C₃ fluoroalkenyl substituted with 0-2
R¹², and aryl substituted with 0-2 R¹²,
or, alternatively, R¹⁰ and R¹¹ may be taken together,
30 with the atoms through which they are attached, to form

a C₃-C₁₀ cycloalkyl group substituted with 0-2 R¹², or ortho-aryl group substituted with 0-2 R¹²;

R¹³ is H or C₁-C₃ alkyl; and

5 Z¹, Z², and Z³ are independently selected from: O, NH, and a direct bond.

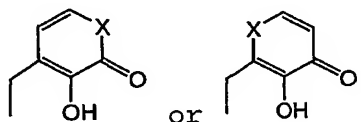
25. A metallopharmaceutical of claim 23 or 24, wherein:

R¹, R², and R³ are -CH₂R⁴;

10 R⁴ is independently elected at each occurrence from: - COOH, -PO₃H₂, -SO₃H, and -C(=O)NR⁶R⁷;

A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:



15

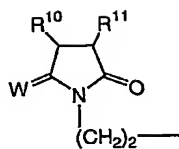
26. A metallopharmaceutical of claim 23 or 24, wherein:

R¹, R², and R³ are -CH₂R⁴;

R⁴ is independently elected at each occurrence from: - COOH, -PO₃H₂, -SO₃H, and -C(=O)NR⁶R⁷;

20 A¹, A², A³, and A⁴ are -(CH₂)₂-; and

Q is a functional group of the formula:



wherein R^{10} and R^{11} are taken together to form a phenyl group substituted with 0-2 R^{12} .

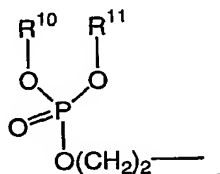
5 27. A metallopharmaceutical of claim 23 or 24, wherein:

R^1 , R^2 , and R^3 are $-\text{CH}_2\text{R}^4$;

R^4 is independently elected at each occurrence from:
 COOH , PO_3H_2 , SO_3H , and $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;

A^1 , A^2 , A^3 , and A^4 are $-(\text{CH}_2)_2-$; and

10 Q is a functional group of the formula:



28. A radiopharmaceutical composition comprising a
 15 metallopharmaceutical of claim 21 and a pharmaceutically acceptable carrier.

29. A method of treating cancer in a patient comprising
 administering to a patient in need thereof a
 20 therapeutically effective amount of a
 radiopharmaceutical composition of claim 28, wherein BM
 is a biologically active targeting molecule selected
 from the group: vitronectin receptor antagonists, growth

factor receptor antagonists, matrix metalloproteinase inhibitors and tyrosine kinase inhibitors.

30. A method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating a radioimage of at least a part of said patient's body;

wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and

M is ^{62}Cu , ^{60}Cu , ^{67}Ga , ^{68}Ga , $^{99\text{m}}\text{Tc}$, or ^{111}In .

31. A method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating a MRI image of at least a part of said patient's body;

wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and

M is paramagnetic metal ion of atomic number 21-29, 42-44 or 58-70.

32. A method of diagnosing thromboembolic disorders or atherosclerosis in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating an X-ray or CT image of at least a part of said patient's body;

wherein BM is a IIb/IIIa receptor ligand or fibrin binding peptide; and

M is heavy metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

5

33. A method of diagnosing infection, inflammation or transplant rejection in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- 10 (ii) generating a radioimage of at least a part of said patient's body;

wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a

15 LTB₄ receptor antagonist; and

M is ⁶²Cu, ⁶⁰Cu, ⁶⁷Ga, ⁶⁸Ga, ^{99m}Tc, or ¹¹¹In.

34. A method of diagnosing infection, inflammation or transplant rejection in a patient, comprising:

- 20 (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating a MRI image of at least a part of said patient's body;

25 wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a LTB₄ receptor antagonist; and

M is paramagnetic metal ion of atomic number 21-29, 42-44 or 58-70.

30

35. A method of diagnosing infection, inflammation or transplant rejection in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating an X-ray or CT image of at least a part of said patient's body;

5 wherein BM is selected from the group consisting of a leukocyte binding peptide, a chemotactic peptide, and a LTB₄ receptor antagonist; and

M is heavy metal ion of atomic number 21-31, 39-49, 50,
10 56-80, 82, 83, 90.

36. A method of detecting new angiogenic vasculature in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating a radioimage of at least a part of said patient's body;

15 wherein BM is a vitronectin receptor antagonist, a somatostatin analog, or a growth factor receptor antagonist; and

20 M is ⁶²Cu, ⁶⁰Cu, ⁶⁷Ga, ⁶⁸Ga, ^{99m}Tc, or ¹¹¹In.

37. A method of detecting new angiogenic vasculature in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating a MRI image of at least a part of said patient's body;

30 wherein BM is a vitronectin receptor antagonist, a somatostatin analog, or a growth factor receptor antagonist; and

M is paramagnetic metal ion of atomic number 21-29, 42-44 or 58-70.

38. A method of detecting new angiogenic vasculature in a patient, comprising:

- (i) administering to said patient a diagnostic effective amount of a metallopharmaceutical of any one of claims 23 to 27; and
- (ii) generating an X-ray or CT image of at least a part of said patient's body;

wherein BM is a vitronectin receptor antagonist, a somatostatin analog, or a growth factor receptor antagonist; and

M is heavy metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, 90.

39. A method of metal detoxification in a patient comprising administering to a patient in need thereof a detoxifying amount of a compound according to claim 1, or a weak chelate complex or salt form thereof, with a pharmaceutically acceptable counterion.

40. A kit for preparing a metallopharmaceutical composition, comprising the following components:

- (i) a conjugate of any one of claims 16 to 20;
- (ii) a pharmaceutically acceptable carrier, a formulating agent, or an adjuvant;
- (iii) a solution of a salt of a metal, or chelate of a metal; and
- (iv) instructions for reacting the components present in the kit;

wherein the metal is selected from the group consisting of a metal ion of atomic number 21-31, 39-49, 50, 56-80, 82, 83, or 90.

- 5 41. A kit for forming a radiopharmaceutical complex comprising the following components:
- (i) a conjugate of any one of claims 16 to 20;
 - (ii) optionally a reducing agent; and
 - (iii) instructions for reacting the components of
- 10 said kit with a radionuclide solution.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/06 C07F5/00 A61K51/04 A61P35/00 A61P29/00
A61K51/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>MISHRA, A. K. ET AL: "Synthesis of macrocyclic bifunctional chelating agents: 1,4,7-tris(carboxymethyl)-10-(2-aminoethyl)-1,4,7,10-tetraazacyclododecane and 1,4,8-tris(carboxymethyl)-11-(2-aminoethyl)-1,4,8,11-tetraazacyclotetradecane"</p> <p>NEW J. CHEM., vol. 25, no. 2, 2001, pages 336-339, XP001011210 page 336</p> <p style="text-align: center;">--- -/--</p>	1-4,6-12

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

2 July 2001

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bader, K

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national Application No

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHAVEZ, MEDARDO R. ET AL: "New route to macrocyclic-based phosphonate acetoxymethyl (AM)-esters: synthesis, cell loading, and ³¹P NMR" retrieved from STN Database accession no. 132:191345 XP002170878 abstract & PROC. SPIE-INT. SOC. OPT. ENG. (1999), 3600(BIOMEDICAL IMAGING: REPORTERS, DYES, AND INSTRUMENTATION), 99-106 ,</p>	1-3,5, 7-11,13
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 374 501 A (DOW CHEMICAL CO) 27 June 1990 (1990-06-27) cited in the application page 14 -page 15; claims 1-20 ---	1,7-9, 16, 21-23, 28-38, 40,41
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30246 A (MITREOAK LIMITED) 16 July 1998 (1998-07-16) page 25	1-3,5, 7-11,13
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 30-38 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 29,39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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